

SERIES IN
MATERNAL-FETAL
MEDICINE

TEXTBOOK OF DIABETES AND PREGNANCY

THIRD EDITION



Edited by

Moshe Hod

Lois G. Jovanovic

Gian Carlo Di Renzo

Alberto De Leiva

Oded Langer



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THIRD EDITION

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Edited by

Moshe Hod MD

Director, Division of Maternal Fetal Medicine
Rabin Medical Center
Sackler Faculty of Medicine, Tel-Aviv University
Petah-Tiqva, Israel

Lois G. Jovanovic MD

Clinical Professor of Medicine, University of Southern California
Keck School of Medicine
Adjunct Professor of Biomolecular Science and Engineering
University of California at Santa Barbara
CEO and Chief Scientific Officer
Sansum Diabetes Research Institute, Santa Barbara, CA, USA

Gian Carlo Di Renzo MD PhD

Professor and Chairman
Department of Obstetrics and Gynecology
Director, Perinatal and Reproductive Medicine Center and Midwifery School, University Hospital
Perugia, Italy
Director, Permanent International and European School of Perinatal and Reproductive Medicine (PREIS)
Florence, Italy

Alberto de Leiva MD PhD

Professor of Medicine, Universitat Autònoma de Barcelona
Director, Department of Endocrinology, Diabetes and Nutrition
Hospital de la Santa Creu i Sant Pau
Principal Investigator, EDUAB-HSP, CIBER-BBN, ISCIII
Vice President and Scientific Director, Fundación DIABEM
Barcelona, Spain

Oded Langer MD PhD

Former Babcock Professor and Chairman
Department of Obstetrics and Gynecology
St. Luke's-Roosevelt Hospital Center
University Hospital for Columbia University
New York, NY, USA



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To the most important people in my life

**My wife Zipi; my sons Roy, Elad, and Yotam; my parents Esther and Michael; my grandchildren Dan,
Guy, Noa, Carmel, and Dor; and their mothers Maya and Timi**

For their tolerance, patience, and love—they made it all possible

Moshe Hod

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Preface

In 2014, the International Federation of Gynecology and Obstetrics (FIGO) embarked on a new gestational diabetes mellitus (GDM) initiative with the ambitious objectives of (1) raising awareness of the links between hyperglycemia and poor maternal and fetal outcomes and to the future health risks to mother and offspring, and demanding a clearly defined global health agenda to tackle this issue, and (2) creating a consensus document that provides guidance for testing, management, and care of women with GDM regardless of resource setting and disseminating and encouraging its use. In order to develop such international guidance, FIGO brought together a group of experts (Moshe Hod, Anil Kapur, David A. Sacks, Eran Hadar, Mukesh Agarwal, Gian Carlo Di Renzo, Luis Cabero Roura, Harold David McIntyre, Jessica L. Morris, and Hema Divakar) to develop a document to frame the issues around gestational diabetes and suggest key actions to address the health burden posed by it. The result—"The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care"—was published in the *International Journal of Gynecology and Obstetrics* 131 (S3) (2015) S173–S211 and launched at the FIGO World Congress in October 2015 in Vancouver.

Despite challenges of providing guidance given the limited high-quality evidence available, this guide outlines current global standards for the testing, management, and care of women with GDM and provides pragmatic recommendations, which, because of their level of acceptability, feasibility, and ease of implementation, have the potential to produce a significant impact. Suggestions are provided for a variety of different regional and resource settings based on their financial, human, and infrastructure resources, as well as for research priorities to bridge the gap between current knowledge and evidence. In assessing the quality of evidence and grading of the strength of recommendations, the guide follows the terminology proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group in which strong recommendations are numbered as 1 and conditional/weak recommendations are numbered 2 with the quality of supporting evidence labeled from very low quality to high quality of evidence.

The guidelines were extremely well received globally but it is the next phase that will be even more challenging for FIGO—the implementation of this extensive document via capacity building, education, and advocacy, as well through establishing a research network which will be able to provide evidence on operational and clinical implementation of the guidelines and provide health economics evidence to support

the cost-effectiveness of the universal diagnosis approach. A summary of the main areas of focus is provided in the following, although we strongly suggest reading the original document, which is open access and includes references and can be found at www.figo.org/figo-project-publications.

Gestational diabetes mellitus

Hyperglycemia is one of the most common medical conditions women encounter during pregnancy, with an estimated one in six live births (16.8%) to women with some form of hyperglycemia in pregnancy. While 16% of these cases may be due to diabetes in pregnancy (either preexisting diabetes—type 1 or type 2—which antedates pregnancy or is first identified during testing in the index pregnancy), the majority (84%) is due to gestational diabetes mellitus (GDM).

The occurrence of GDM parallels the prevalence of impaired glucose tolerance (IGT), obesity, and type 2 diabetes mellitus (T2DM) in a given population. These conditions are on the rise globally. Moreover, the age of onset of diabetes and pre-diabetes is declining while the age of childbearing is increasing. There is also an increase in the rate of overweight and obese women of reproductive age; thus, more women entering pregnancy have risk factors that make them vulnerable to hyperglycemia during pregnancy.

GDM is associated with a higher incidence of maternal morbidity, including cesarean deliveries, shoulder dystocia, birth trauma, hypertensive disorders of pregnancy (including pre-eclampsia), and subsequent development of T2DM. Perinatal and neonatal morbidities also increase; the latter include macrosomia, birth injury, hypoglycemia, polycythemia, and hyperbilirubinemia. Long-term sequelae in offspring with in utero exposure to maternal hyperglycemia may include higher risks for obesity and diabetes later in life.

In most parts of low- and middle-income countries (LMICs) (which contribute to over 85% of the annual global deliveries), most women are either not screened or improperly screened for diabetes during pregnancy—despite these countries accounting for 80% of the global diabetes burden and for 90% of all cases of maternal and perinatal deaths and poor pregnancy outcomes. In particular, eight LMICs—India, China, Nigeria, Pakistan, Indonesia, Bangladesh, Brazil, and Mexico—account for 55% of the global live births (70 million live births annually) and 55% of the global burden of diabetes (209.5 million) and should be key targets for any focused strategy on addressing the global burden of GDM pregnancies. These countries have been identified as priority countries for all future GDM interventions.

Given the interaction between hyperglycemia and poor pregnancy outcomes, the role of in utero imprinting in increasing the risk of diabetes and cardiometabolic disorders in the offspring of mothers with hyperglycemia in pregnancy, and increasing maternal vulnerability to future diabetes and cardiovascular disorders, there needs to be a greater global focus on preventing, screening, diagnosing, and managing hyperglycemia in pregnancy. The relevance of GDM as a priority for maternal health and its impact on the future burden of noncommunicable diseases is no longer in doubt, but how best to deal with the issue remains contentious, as there are many gaps in knowledge on how to prevent, diagnose, and manage GDM to optimize care and outcome. These must be addressed through future research.

Diagnosing GDM

Global healthcare organizations and professional bodies have advocated a plethora of diverse algorithms for screening and diagnosis of GDM that have been criticized for lacking validation, inasmuch as they were developed based on tenuous data, the biased result of expert opinions, which were based on economic considerations or were convenience oriented, thereby creating confusion and uncertainty among care providers. One underlying yet fundamental problem, as shown consistently by several studies, including the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, is that the risk of poor pregnancy outcomes associated with hyperglycemia is continuous, with no clear inflection points.

It is therefore clear that any set of criteria for the diagnosis of GDM proposed will need to evolve from a consensus approach, balancing risks and benefits in particular social, economic, and clinical contexts. In addition to different cut-off values, the lack of consensus among different professional bodies for an algorithm for screening and diagnosis of GDM is perhaps an even larger problem.

Selective testing based on clinical risk factors for GDM evolved from the view that in populations with a low risk of GDM, subjecting all pregnant women to a laboratory test was not considered cost-effective. Variations in risk factors have resulted in different approaches, generally with poor sensitivity and specificity. The major problem of risk factor-based screening is its high demand on healthcare providers with more complex protocols for testing, which result in lower compliance by both patients and healthcare providers.

Given the high rates of hyperglycemia in pregnancy in most populations and that selective testing based on known risk factors has poor sensitivity for detection of GDM in a given population, it seems appropriate to recommend universal rather than risk factor-based testing. This approach is strongly recommended by FIGO and is particularly relevant to LMICs where 90% of all cases of GDM are found and ascertainment of risk factors is poor owing to low levels of education and awareness and poor record keeping. In many of these countries, there is little justification for selective testing, as they also have ethnic populations considered to

be at high risk, and universal testing will have to be strictly implemented and measured to ensure that all women are offered the test.

The diagnosis of diabetes in pregnancy as defined by the WHO criteria and the diagnosis of GDM should be made using a single-step 75 g OGTT as per the recommendation of the IADPSG (2010) and WHO (2013). FIGO suggests various alternatives based on resource settings in Table P.1.

Glucose measurement: Technical considerations in laboratory and point-of-care testing

Most glucose measurements in laboratories are performed on serum or plasma. Faster laboratory turnaround time is one reason that plasma has become the gold standard for glucose measurement. However, in most laboratory panels (i.e., the comprehensive metabolic panel), serum is the most suitable sample for all other laboratory tests performed, and so a “panel” glucose is usually a serum glucose.

Ideally, for diagnosis of GDM, reliable test results should be based on venous plasma samples properly collected and transported prior to laboratory testing by an accredited laboratory. However, this ideal situation may not be present in many primary care settings, particularly in the developing world where proper facility for collection, transport, storage, or testing may not exist. In this situation, FIGO recommends that it is acceptable to use a plasma calibrated handheld glucometer with properly stored test strips to measure plasma glucose. Regular calibration should be undertaken with standard test solutions (usually supplied by the glucose meter manufacturer).

Management of hyperglycemia during pregnancy

Fetal and maternal outcomes are directly correlated with the degree of maternal glycemic control. The primary goal of treatment for pregnancies complicated by diabetes is to ensure as close to normal outcome as possible for the mother and offspring by controlling maternal hyperglycemia. Since fetal macrosomia is the most frequent complication of diabetes, special effort should be directed toward its diagnosis and prevention. Fetal assessment can be achieved by a fetal kick count, biophysical profile, and cardiotocography (nonstress test).

Maternal hyperglycemia and macrosomia are associated with increased risk of intrauterine fetal death and other adverse outcomes. Therefore, induction of labor may be considered at 38–39 weeks, although there is no good-quality evidence to support such an approach. Thus, some guidelines suggest that a pregnancy with good glycemic control and a seemingly appropriate gestational-age fetus ought to continue until 40–41 weeks. Given the significantly greater

Table P.1 Options for diagnosis of GDM based on resource settings

Setting	Strategy			
	Who to test and when	Diagnostic test	Interpretation ^a	Grade
Fully resourced settings	All women at booking/first trimester 24–28 weeks	Measure FPG, RBG, or HbA1c to detect diabetes in pregnancy If negative: perform 75 g 2-hour OGTT		1 ⊕⊕⊕⊕
Fully resourced settings serving ethnic populations at high risk ^b	All women at booking/first trimester 24–28 weeks	Perform 75 g 2-hour OGTT to detect diabetes in pregnancy If negative: repeat 75 g 2-hour OGTT		2 ⊕⊕⊕⊕
Any setting (basic); particularly medium- to low-resource settings serving ethnic populations at risk	All women between 24 and 28 weeks	Perform 75 g 2-hour OGTT		1 ⊕⊕⊕⊕
<i>Alternative strategies as currently used in specified countries</i>				
China: Medium- to low-resource settings serving populations at high risk	All women at booking/first trimester	Measure FPG to detect diabetes in pregnancy	>7.0 mmol/L or >126 mg/dL. FPG values between 5.6 and 6.9 mmol/L (100 and 125 mg/dL) consider as GDM	2 ⊕⊕⊕⊕
	24–28 weeks	If negative: perform 75 g 2-hour OGTT <i>Or</i> To reduce number of OGTTs measure FPG. Only in women with values between 4.5 and 5.0 mmol/L (81 and 90 mg/dL) perform 75 g 2-hour OGTT	Value >5.1 mmol/L or >92 mg/dL diagnostic of GDM	1 ⊕⊕⊕⊕
				2 ⊕⊕⊕⊕
Indian subcontinent: Medium- to low-resource settings serving rural/semi-urban/urban ethnic populations at high risk	All women at booking/first trimester	Measure fasting or nonfasting 2-hour value after 75 g OGTT	Reading between 7.8 and 11.0 mmol/L or 140 and 199 mg/dL indicates GDM	2 ⊕⊕⊕⊕
	24–28 weeks	If negative: repeat test		
Latin America: Medium- to low-resource settings	All women at booking/first trimester	Measure FPG to detect diabetes in pregnancy	>7.0 mmol/L or >126 mg/dL. FPG values between 5.6 and 6.9 mmol/L (100 and 125 mg/dL) consider as GDM	2 ⊕⊕⊕⊕
	24–28 weeks	If negative: perform 75 g 2-hour OGTT	75 g 2-hour glucose value >7.8 mmol/L or >140 mg/dL is diagnostic of GDM ^d	

(Continued)

Table P.1 (Continued) Options for diagnosis of GDM based on resource settings

Setting	Strategy			Grade
	Who to test and when	Diagnostic test	Interpretation ^a	
United Kingdom: All settings	Selected women at booking/as soon as possible ^e	Perform 75 g 2-hour OGTT	FPG of 100 mg/dL or 5.6 mmol/L or above or 2-hour plasma glucose of 140 mg/dL or 7.8 mmol/L or above is diagnostic ^g	
	24–28 weeks Offered also to other women with risk factors for GDM ^f	If negative: perform 75 g 2-hour OGTT		
<i>Abbreviations:</i> FPG, fasting plasma glucose; RBG, random blood glucose; HbA1c, glycosylated hemoglobin; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test. ^a Interpret as per IADPSG/WHO/IDF guidelines unless stated otherwise. ^b Asians are at high risk of hyperglycemia during pregnancy, which may include previously undiagnosed diabetes. The proportion of previously undiagnosed diabetes is highest in the youngest age group particularly among women. In Asian populations, FPG and HbA1c have much lower sensitivity to diagnose diabetes than the 2-hour post-glucose value. In a study of 11 Asian cohorts, more than half of the diabetic subjects had isolated postchallenge hyperglycemia. In a study in China, 46.6% of the participants with undiagnosed diabetes (44.1% of the men and 50.2% of the women) had isolated increased 2-hour plasma glucose levels after an OGTT. Therefore, the need to identify postprandial hyperglycemia seems especially relevant in Asian populations. ^c Diabetes in Pregnancy Study Group in India (DIPSI) Guideline. ^d Latin America Study Group. ^e Women with a past history of GDM or women with glycosuria of 2+ or above on one occasion or of 1+ or above on two or more occasions (as detected by reagent strip testing during routine prenatal care in the current pregnancy). ^f BMI above 30 (calculated as weight in kilograms divided by height in meters squared), previous macrosomic baby weighing 4.5 kg or above, family history of diabetes, first-degree relative with diabetes, minority ethnic family origin with a high prevalence of diabetes. ^g National Institute for Health and Care Excellence (NICE) Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. NICE guidelines [NG3]. Published February 2015. http://www.nice.org.uk/guidance/ng3/evidence.				

risk of shoulder dystocia at any birthweight above 3750 g for babies of women with diabetes, consideration may be given to elective cesarean delivery when the best estimate of fetal weight exceeds 4000 g. Recommendations are provided for prenatal supervision, fetal growth assessment, fetal well-being surveillance, and timing and mode of delivery.

Blood glucose control can be evaluated in one of three ways: glycosylated hemoglobin (HbA1c), self-monitoring of blood glucose, and continuous glucose monitoring. The recommendations for glucose monitoring in women with GDM are given in the document. Attempts must be made to achieve glucose levels as close as possible to those seen in normal pregnancy. Elevated glucose values, specifically postprandial glucose levels, are associated with adverse pregnancy outcomes in patients with hyperglycemia in pregnancy. Data suggest that postprandial glucose levels are more closely associated with macrosomia than fasting glucose levels. No controlled study has, as yet, established the optimal plasma glucose level(s) to prevent increased fetal risk. Glycemic targets for women with GDM are provided.

Overweight and obese women before pregnancy are at an increased risk for pregnancy complications including

diabetes, hypertensive complications, stillbirth, and cesarean delivery. Recommendations are given for weight gain during pregnancy for women with diabetes. Nutritional therapy includes an individualized food plan to optimize glycemic control. It should be based on personal and cultural eating habits, physical activity, blood glucose measurements, and the expected physiological effects of pregnancy on the mother and her fetus. Nutritional intervention for diabetes, specifically pregnancy complicated with diabetes, is consistently considered a fundamental treatment modality and is the first-line therapy for all women diagnosed with GDM. Women with GDM and DIP must receive practical education that empowers them to choose the right quantity and quality of food. Recommendations are given for nutrition therapy in women with GDM, and for physical activity, which has been shown to have benefits.

Management using pharmacological treatment may also be required. In the short term, for women with GDM requiring drug treatment, glyburide is inferior to both insulin and metformin, while metformin (plus insulin when required) performs slightly better than insulin. Recommendations for pharmacological treatment in women with GDM are

given. It is important to note that there is no long-term evidence on the safety of oral antidiabetic drugs (OADs). The following insulins may be considered safe and effective treatment during pregnancy: regular insulin, NPH, lispro, aspart, and detemir.

Postpartum management

The postpartum period is crucial, not only in terms of addressing the immediate perinatal problems but also in the long term for establishing the basis for early preventive health for both mother and child, who are at a heightened risk for future obesity, metabolic syndrome, diabetes, hypertension, and cardiovascular disorders.

Mothers with GDM and diabetes in pregnancy need to be encouraged and supported in initiating and maintaining breastfeeding. Breastfeeding has been shown to be protective against the occurrence of infant and maternal complications, including reduction in childhood obesity, T2DM, and even T1DM. Moreover, breastfeeding helps postpartum weight loss. Treatment with insulin or commonly used OADs, such as glyburide and metformin, is not a contraindication to breastfeeding as levels of OAD medications in breast milk are negligible and do not cause hypoglycemia in the baby.

For all women diagnosed with hyperglycemia for the first time during pregnancy (GDM and DIP), the glycemic status should be reevaluated with a 75 g oral OGTT at 6–12 weeks after delivery with diagnosis based on the WHO criteria for diabetes, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) in the nonpregnant state. Women who do not have diabetes or pre-diabetes, according to these definitions, are still at risk of progression to diabetes and other cardiovascular problems and require ongoing surveillance according to local protocol.

Irrespective of the glycemic status on early postpartum testing, it should be assumed that women with GDM have the same or a higher level of future risk of diabetes and cardiovascular disease as people with prediabetes and they should be advised to maintain a healthy lifestyle with an appropriate diet, regular exercise, and normal body weight. Furthermore, to ensure optimal health before attempting their next pregnancy, they should seek consultation with healthcare providers knowledgeable about diabetes prevention. Progression to diabetes is more common in women with a history of GDM compared with those without GDM history, despite equivalent degrees of IGT at baseline. Both intensive lifestyle and metformin have been shown to be highly effective in delaying or preventing diabetes in women with IGT and a history of GDM and lowering the risk of progression from GDM to T2DM.

Obstetricians, family physicians, internists, pediatricians, and other healthcare providers must link postpartum follow-up of a GDM mother with the child's vaccination and routine pediatric care program to ensure continued follow-up and engagement of the high-risk mother–child pair.

Preconception care

Preconception care is a set of assessment measures and interventions undertaken prior to conception. These are aimed at identifying and modifying medical, behavioral, and social risks to women's health during pregnancy, which may prevent or mitigate adverse pregnancy outcomes.

Pregnancies should be planned and maternal assessment with possible interventions should occur prior to conception to improve pregnancy outcome and maternal health. This may not only improve immediate maternal, perinatal, and neonatal outcomes, but possibly may have long-term beneficial effects on both the mother and her baby, lasting well into adulthood and impacting next-generation offspring, through epigenetic changes and intrauterine fetal programming. It is estimated that 30%–90% of women have at least one condition or risk factor, such as anemia, undernutrition, obesity, diabetes, hypertension, and thyroid disorders, that may benefit from an appropriate preconception intervention; however, only 30%–50% of pregnancies are planned and receive proper preconception care. The key challenges are increasing awareness and acceptance of the concept of preconception counseling and increasing affordability and access to preconception services to women of reproductive age.

Universal preconception care, as a concept, is still a challenge in most parts of the world, where a significant proportion of women do not have access to prenatal care or receive only one or two prenatal visits, the concept of preconception care is a far-off goal but envisaged as an intervention that could dramatically change maternal and neonatal health and outcomes. Screening for conditions such as malnutrition, anemia, overweight and obesity, hypertension, diabetes, and thyroid dysfunction may have a significant impact. For women with diabetes, preconception care is also cost-saving and yet only half the women with diabetes undergo appropriate preconception glycemic control.

In summary, to address the issue of GDM, FIGO recommends the following:

- *Public health focus:* There should be greater international attention paid to GDM and to the links between maternal health and noncommunicable diseases on the sustainable developmental goals agenda. Public health measures to increase awareness, access, affordability, and acceptance of preconception counseling, and prenatal and postnatal services for women of reproductive age must be prioritized.
- *Universal testing:* All pregnant women should be tested for hyperglycemia during pregnancy using a one-step procedure and FIGO encourages all countries and its member associations to adapt and promote strategies to ensure this.
- *Criteria for diagnosis:* The WHO criteria for diagnosis of diabetes mellitus in pregnancy and the WHO and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria for diagnosis of GDM should be used when possible. Keeping in mind the resource

constraints in many low-resource countries, alternate strategies described in the document should also be considered equally acceptable.

- *Diagnosis of GDM:* Diagnosis should ideally be based on laboratory results of venous plasma samples that are properly collected, transported, and tested. Given the resource constraints in many low-resource countries, it is acceptable to use a plasma-calibrated handheld glucometer for diagnostic purposes.
- *Management of GDM:* Management should be in accordance with available national resources and infrastructure even if the specific diagnostic and treatment protocols are not supported by high-quality evidence, as this is preferable to no care at all.
- *Lifestyle management:* Nutrition counseling and physical activity should be the primary tools in the management of GDM. Women with GDM must receive practical nutritional education and counseling that will empower them to choose the right quantity and quality of food and level of physical activity. They should be advised repeatedly during pregnancy to continue the same healthy lifestyle after delivery to reduce the risk of future obesity, T2DM, and cardiovascular diseases.
- *Pharmacological management:* If lifestyle modification alone fails to achieve glucose control, metformin, glyburide, or insulin should be considered as safe and

effective treatment options for GDM during the second and third trimesters.

- *Postpartum follow-up and linkage to care:* Following a GDM pregnancy, the postpartum period provides an important platform to initiate beneficial health practices for both mother and child to reduce the future burden of several noncommunicable diseases. Obstetricians must establish links with family physicians, internists, pediatricians, and other healthcare providers to support postpartum follow-up of GDM mothers and their children. A follow-up program linked to the child's vaccination and regular health check-up visits provides an opportunity for continued engagement with the high-risk mother-child pair.
- *Future research:* There should be greater international research collaboration to address the knowledge gaps to better understand the links between maternal health and noncommunicable diseases. Evidence-based findings are urgently needed to provide best practice standards for testing, management, and care of women with GDM. Cost-effectiveness models must be used in countries with specific burden of disease and resources to make the best choices for testing and management of GDM.

Moshe Hod

Contributors

Salvatore Alberico

Unit of Obstetrical Pathology
Institute for Maternal and Child Health
IRCCS “Burlo Garofolo”
Trieste, Italy

Raul Artal

Department of Obstetrics, Gynecology and
Women’s Health
School of Medicine
Saint Louis University
St. Louis, Missouri

Sabaratnam Arulkumaran

St George’s University of London
London, United Kingdom

Eran Ashwal

Rabin Medical Center
Helen Schneider Hospital for Women
Petah Tikva, Israel

and

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Amir Aviram

Helen Schneider Hospital for Women
Rabin Medical Center
Petah Tikva, Israel

and

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Giulia Babucci

Department of Gynecology
and
Centre of Perinatal and Reproductive
Medicine
University of Perugia
Perugia, Italy

Komal Bajaj

Department of Obstetrics and Gynecology
Albert Einstein College of Medicine
Bronx, New York

Jacob Bar

Department of Obstetrics & Gynecology
Edith Wolfson Medical Center
Holon, Israel

and

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Helen Lorraine Graham Barrett

Royal Brisbane and Women’s Hospital
Herston, Queensland, Australia

Ahmet A. Baschat

Department of Obstetrics, Gynecology and
Reproductive Sciences
School of Medicine
University of Maryland
Baltimore, Maryland

Itai Ben-David

General Intensive Care Department and
Institute for Nutrition Research
Beilinson Hospital
Rabin Medical Center
Petah Tikva, Israel

and

Sackler School of Medicine
Tel Aviv University
Tel Aviv, Israel

Rhonda Bentley-Lewis

Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Noa Bischitz

Laboratory of Teratology
Hadassah Medical School
Hebrew University
Israeli Ministry of Health
Jerusalem, Israel

Bartolomé Bonet

Department of Pediatrics
Universitat Illes Balears
Illes Balears, Spain

and

Servicio de Pediatría
Hospital Can Misses
Ibiza, Spain

María Bonet-Alavés

Universitat Illes Balears
Illes Balears, Spain

and

Servicio de Pediatría
Hospital Can Misses
Ibiza, Spain

Matteo Andrea Bonomo

Diabetes Unit
Niguarda Ca’ Granda Hospital
Milano, Italy

Laura D. Brown

Department of Pediatrics
School of Medicine
University of Colorado
Aurora, Colorado

Eulàlia Brugués

Fundación DIABEM
Barcelona, Spain

Luis Cabero

Hospital Vall de Hebron
Universitat Autònoma de Barcelona
Barcelona, Spain

Leonie Kaye Callaway

Department of Obstetric Medicine
University of Queensland
Brisbane, Queensland, Australia

and

Royal Brisbane and Women’s Hospital
Herston, Queensland, Australia

Roberta Carboni

Neonatal Intensive Care Unit
Puericulture Institute and Neonatal Section
Azienda Ospedaliera Universitaria
University of Cagliari
Cagliari, Italy

Ron Charach

Department of Obstetrics and Gynecology
Soroka University Medical Center
Ben-Gurion University of the Negev
Beer Sheva, Israel

Lisa Chasan-Taber

Division of Biostatistics and Epidemiology
School of Public Health and Health Sciences
University of Massachusetts
Amherst, Massachusetts

Graziano Clerici

Department of Gynecology
and
Centre of Perinatal and Reproductive
Medicine
University of Perugia
Perugia, Italy

Rosa Corcoy

Universitat Autònoma de Barcelona
and
Diabetes Unit
Department of Endocrinology, Diabetes and
Nutrition
Hospital de la Santa Creu i Sant Pau
Barcelona, Spain

Donald R. Coustan

Division of Maternal-Fetal Medicine
Brown University
Providence, Rhode Island

Maria Grazia Dalfrà

DPT Medicine
UOC Diabetology and Dietetic
Padova University
Padova, Italy

Peter Damm

Faculty of Health and Medical Sciences
Center for Pregnant Women with Diabetes,
Rigshospitalet
The Institute of Clinical Medicine
and
Department of Obstetrics, Rigshospitalet
University of Copenhagen
Copenhagen, Denmark

Harold W. de Valk

Department Internal Medicine
University Medical Center
Utrecht, the Netherlands

Marloes Dekker-Nitert

School of Medicine
Centre for Clinical Research
University of Queensland
Brisbane, Queensland, Australia

Alberto de Leiva

Universitat Autònoma de Barcelona
and
Department of Endocrinology, Diabetes and
Nutrition
Hospital de la Santa Creu i Sant Pau
and
EDUAB-HSP, CIBER-BBN, ISCIII
and
Fundación DIABEM
Barcelona, Spain

Alejandra de Leiva-Pérez

Fundación DIABEM
and
Universitat Oberta de Catalunya
Barcelona, Spain

Fiona C. Denison

Tommy's Centre for Maternal and Fetal
Health
MRC/University of Edinburgh Centre for
Reproductive Health
Queen's Medical Research Institute
Edinburgh, United Kingdom

Gernot Desoye

Department of Obstetrics and Gynaecology
Medical University of Graz
Graz, Austria

Angelica Dessì

Neonatal Intensive Care Unit
Puericulture Institute and Neonatal Section
Azienda Ospedaliera Universitaria
University of Cagliari
Cagliari, Italy

Graziano Di Cianni

Diabetes and Metabolic Diseases Unit
Livorno Hospital
Livorno, Italy

Gian Carlo Di Renzo

Department of Obstetrics and Gynecology
and
Perinatal and Reproductive Medicine Center
and Midwifery School
University Hospital
Perugia, Italy

and

Permanent International and European
School of Perinatal and Reproductive
Medicine (PREIS)
Florence, Italy

Celeste P. Durnwald

Division of Maternal Fetal Medicine
Department of Obstetrics and Gynecology
University of Pennsylvania
Philadelphia, Pennsylvania

Ulf J. Eriksson

Department of Medical Cell Biology
Biomedical Center
Uppsala University
Uppsala, Sweden

Vassilios Fanos

Neonatal Intensive Care Unit
Puericulture Institute and Neonatal Section
Azienda Ospedaliera Universitaria
University of Cagliari
Cagliari, Italy

Maria Farren

UCD Centre for Human Reproduction
Coombe Women and Infant's University
Hospital
Dublin, Ireland

Denice S. Feig

Department of Medicine, Obstetrics and
Gynecology
and
Department of Health Policy, Management
and Evaluation
University of Toronto
and
Division of Endocrinology and Metabolism
Mount Sinai Hospital
Toronto, Ontario, Canada

Francesc Figueras

Barcelona Center of Maternal-Fetal Medicine
and Neonatology
Hospital Clinic and Hospital Sant Joan de Deu
University of Barcelona
and
Centre for Biomedical Research on Rare
Diseases
Barcelona, Spain

Rinat Gabbay-Benziv

Helen Schneider Hospital for Women
Rabin Medical Center
Petah Tikva, Israel

Ronni Gamzu

Tel Aviv Sourasky Medical Center
Tel Aviv University
Tel Aviv, Israel

Eduard Gratacós

Hospital Clinic i Hospital Sant Joan de Deu
Universitat de Barcelona
Barcelona, Spain

Susan J. Gross

Albert Einstein College of Medicine
Bronx, New York
and
Natera, Inc.
San Carlos, California

Eran Hadar

Rabin Medical Center
Helen Schneider Hospital for Women
Petah Tikva, Israel

and

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

David R. Hadden (deceased)

Regional Endocrinology and Diabetes
Centre
Royal Victoria Hospital
Northern Ireland, United Kingdom

Ilana Jaye Halperin

Division of Endocrinology and Metabolism
Department of Medicine
Sunnybrook Health Sciences Centre
University of Toronto
Toronto, Ontario, Canada

Mark A. Hanson

Institute of Developmental Sciences
Southampton General Hospital
Southampton, United Kingdom

Avi Ben Haroush

Department of Obstetrics and Gynecology
Helen Schneider Hospital for Women
Rabin Medical Center
Petah Tikva, Israel

William W. Hay, Jr.

School of Medicine
University of Colorado
Aurora, Colorado

Emilio Herrera

Faculties of Pharmacy and Medicine
Universidad CEU San Pablo
Madrid, Spain

Liran Hiersch

Lis Hospital for Women
Tel Aviv Sourasky Medical Center
Tel Aviv University
Petah Tikva, Israel

Moshe Hod

Department of Obstetrics and Gynecology
Helen Schneider Hospital for Women
Rabin Medical Center
Petah Tikva, Israel

and

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Berthold Huppertz

Institute of Cell Biology, Histology and
Embryology
Medical University of Graz
Graz, Austria

Lois Jovanovic

Keck School of Medicine
University of Southern California
Los Angeles, California

and

University of California, Santa Barbara
and
Sansum Diabetes Research Institute
Santa Barbara, California

James G. Kahn

Philip R. Lee Institute for Health Policy
Studies
Global Health Sciences
and
Global Health Economics Consortium
University of California, San Francisco
San Francisco, California

Ofra Kalter-Leibovici

Gertner Institute for Epidemiology and
Health Policy Research
Ramat Gan, Israel

Anil Kapur

World Diabetes Foundation
Gentofte, Denmark

John L. Kitzmiller

Good Samaritan Hospital
San Jose, California

and

Sansum Medical Research Institute
Santa Barbara, California

Michal Kovo

Department of Obstetrics and Gynecology
Edith Wolfson Medical Center
Holon, Israel

and

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Aaron Kowalski

Juvenile Diabetes Research Foundation
New York, New York

Emilia Lacaria

Diabetes and Metabolic Diseases Unit
Livorno Hospital
Livorno, Italy

Mark B. Landon

Department of Obstetrics and Gynecology
College of Medicine
The Ohio State University
Columbus, Ohio

Oded Langer

Department of Obstetrics and Gynecology
St. Luke's–Roosevelt Hospital Center
and
University Hospital for Columbia University
New York, New York

Annunziata Lapolla

DPT Medicine
UOC Diabetology and Dietetic
Padova University
Padova, Italy

Cristina Lencioni

Diabetes and Metabolic Diseases Unit
Livorno Hospital
Livorno, Italy

Nicky Lieberman

Community Medicine Division
Clalit Health Services
Tel Aviv, Israel

Nicolai Lohse

Department of Anesthesia
Copenhagen University Hospital,
Rigshospitalet
Copenhagen, Denmark

Rahat Maitland

Division of Women's Health
King's College
London, United Kingdom

Elliot Marseille

Health Strategies International
Oakland, California

and

Global Health Economics Consortium
University of California, San Francisco
San Francisco, California

Gianpaolo Maso

Unit of Obstetrical Pathology
Institute for Maternal and Child Health
IRCCS "Burlo Garofolo"
Trieste, Italy

Elisabeth R. Mathiesen

Faculty of Health and Medical Sciences
Center for Pregnant Women with Diabetes,
Rigshospitalet
The Institute of Clinical Medicine
and
Faculty of Health Sciences, Rigshospitalet
Department of Endocrinology
University of Copenhagen
Copenhagen, Denmark

Dídac Mauricio

Department of Endocrinology and Nutrition
Hospital Germans Trias i Pujol
Universitat Autònoma de Barcelona
Badalona, Spain

Harold David McIntyre

University of Queensland
St. Lucia, Queensland, Australia

and

Mater Health Services
South Brisbane, Queensland. Australia

Federico Mecacci

Obstetrical Pathology Department and High
Risk Pregnancy Unit
University of Florence
Florence, Italy

Hamutal Meiri

ASPRE
Tel Aviv, Israel

Nir Melamed

Department of Obstetrics/Gynecology
Rabin Medical Center
Petah Tikva, Israel

Giorgio Mello

Obstetrical Pathology Department and High
Risk Pregnancy Unit
University of Florence
Florence, Italy

Paul Merlob

Department of Neonatology
Schneider Children Hospital
Petah Tikva, Israel

and

Sackler School of Medicine
Tel Aviv University
Tel Aviv, Israel

Boyd E. Metzger

Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Delphine Mitanchez

Division of Neonatology
Department of Perinatology
Armand Trousseau Hospital
Sorbonne Universités
University Pierre et Marie Curie
Paris, France

Helen R. Murphy

Wellcome Trust-MRC Institute of Metabolic
Science
University of Cambridge Metabolic Research
Laboratories
and
NIHR Cambridge Biomedical Centre
Addenbrooke's Hospital
Cambridge, United Kingdom

Angela Napoli

Department of Clinical and Molecular
Medicine
Sapienza University of Rome
Roma, Italy

Kypros Nicolaides

The Fetal Medicine Foundation
London, United Kingdom

Jeremy Oats

Melbourne School of Population and
Global Health
University of Melbourne
Burnley, Victoria, Australia

Sara Ornaighi

Department of Obstetrics and Gynecology
University of Milano-Bicocca
Monza, Italy

and

Department of Obstetrics, Gynecology and
Reproductive Sciences
Yale Women and Children's Center for
Blood Disorders and Preeclampsia
Advancement
Yale University
New Haven, Connecticut

Asher Ornoy

Laboratory of Teratology
Hadassah Medical School
Hebrew University
Israeli Ministry of Health
Jerusalem, Israel

Henar Ortega-Senovilla

Faculties of Pharmacy and Medicine
Universidad CEU San Pablo
Madrid, Spain

Michael J. Paidas

Department of Obstetrics, Gynecology and
Reproductive Sciences
Yale University
New Haven, Connecticut

Lucilla Poston

Department of Life Sciences and Medicine
King's College London
London, United Kingdom

Marlon Pragnell

Juvenile Diabetes Research Foundation
New York, New York

Marianna Pina Rambaldi

Obstetrical Pathology Department and High
Risk Pregnancy Unit
University of Florence
Florence, Italy

Maria Rosaria Raspollini

Division of Histology and Molecular
Diagnostics
University of Florence
Florence, Italy

Rebecca M. Reynolds

Endocrinology Unit
UoE/BHF Centre for Cardiovascular
Science
Queen's Medical Research Institute
Edinburgh, United Kingdom

Lene Ringholm

Faculty of Health and Medical Sciences
Center for Pregnant Women with Diabetes,
Rigshospitalet
The Institute of Clinical Medicine
and
Department of Endocrinology
University of Copenhagen
Copenhagen, Denmark

Drucilla Roberts

Department of Pathology
Harvard Medical School,
Massachusetts General Hospital
Boston, Massachusetts

Paul J. Rozance

Department of Pediatrics
School of Medicine
University of Colorado
Aurora, Colorado

Laura Russo

Diabetes and Metabolic Diseases Unit
Livorno Hospital
Livorno, Italy

Isabel Sánchez-Vera

School of Medicine
University San Pablo
and
School of Pharmacy
Urb Montepincipe
Boadilla del Monte
Madrid, Spain

Eyal Sheiner

Faculty of Health Sciences
Department of Obstetrics and Gynecology
Soroka University Medical Center
Ben-Gurion University of the Negev
Beer Sheva, Israel

Anat Shmueli

Rabin Medical Center
Tel Aviv University
Petah Tikva, Israel

Umberto Simeoni

Faculté de Pharmacie
Marseille-University
Marseille, France

and

Division of Pediatrics
and
DOHaD Research Unit
University of Lausanne
Lausanne, Switzerland

Pierre Singer

General Intensive Care Department and
Institute for Nutrition Research
Beilinson Hospital
Rabin Medical Center
Petah Tikva, Israel
and
Sackler School of Medicine
Tel Aviv University
Tel Aviv, Israel

Gabriella Solomon

Community Medical Division
Clalit Health Services
Tel Aviv, Israel

Zoe A. Stewart

Wellcome Trust-MRC Institute of Metabolic
Science
University of Cambridge Metabolic Research
Laboratories
and
NIHR Cambridge Biomedical Research Centre
Addenbrooke's Hospital
Cambridge, United Kingdom

Rina Su

Department of Obstetrics and Gynecology
Peking University First Hospital
Beijing, People's Republic of China

Kinneret Tenenbaum-Gavish

Rabin Medical Center
Tel Aviv University
Petah Tikva, Israel

Yoel Toledano

Division of Maternal Fetal Medicine
Helen Schneider Hospital for Women
Rabin Medical Center
Petah Tikva, Israel

Michael Turner

UCD Centre for Human Reproduction
Coombe Women and Infant's University
Hospital
Dublin, Ireland

Gerard H.A. Visser

Department of Obstetrics
Wilhelmina Children's Hospital
University Medical Center
Utrecht, the Netherlands

Tuangsit Wataganara

Faculty of Medicine Siriraj Hospital
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Mahidol University
Bangkok, Thailand

Louise K. Weile

Department of Gynaecology and Obstetrics
Odense University Hospital
Odense, Denmark

Parri Wentzel

Department of Medical Cell Biology
Biomedical Center
Uppsala University
Uppsala, Sweden

Stephanie R. Wesolowski

Department of Pediatrics
School of Medicine
University of Colorado
Aurora, Colorado

Huixia Yang

Department of Obstetrics and Gynecology
Peking University First Hospital
Beijing, People's Republic of China

Yariv Yogev

Helen Schneider Hospital for Women
Rabin Medical Center
Petah Tikva, Israel

and

Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Catherine Zyzdorzcyk

Faculté de Pharmacie
Aix-Marseille University
Marseille, France

Weiwei Zhu

National Institute of Hospital Administration
Beijing, People's Republic of China

Moshe Zloczower

Bruce Rappaport Faculty of Medicine
Endocrine Department and Diabetes in
Pregnancy Clinic
Technion—Israel Institute of Technology
Haifa, Israel

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1 Introduction: Merging the legacies and hypotheses—Maternal medicine meets fetal medicine

Moshe Hod, Kypros Nicolaides, Hamutal Meiri, and Nicky Lieberman

Introduction

This chapter was written in line with the need to revolutionize maternal fetal medicine by returning the M (maternal) to the MFM subspecialty (maternal–fetal medicine) by introducing a new paradigm of care composed of novel technologies and comprehensive services in order to reduce maternal and fetal morbidity and mortality. A three-floor service model is introduced, composed of the prepregnancy clinic, the inverted pyramid of antenatal care, and the postpregnancy clinic, each with a combined methodology composed of existing and novel testing procedures (such as preglycemic evaluation in the prepregnancy clinic, free circulating DNA during the first trimester, or echocardiography of the newborn in the postnatal service, among many others). All floors begin at the level of community clinic/family obstetrician before the high-risk specialists are called to service and introduce a contingency management and prevention follow-up. The approach expresses the need to provide comprehensive service starting from a traditional patient evaluation spanning medical and pregnancy history and demography, biochemical and biophysical markers, sonography, chemical blood tests, and introducing “omics” to fetal medicine. This approach enables personalized medicine and a systematic method to focus the medical attention on those who need it most, allowing the others to have a less intensive medical involvement. It fits the new world of social media, computerized algorithms derived from mega databases, and the need to integrate all sources of information and know-how to generate an evidence-based medical treatment plan as required in today’s world of medicine. This chapter calls for introducing training and education to the new doctor generation and to systematically adjust the maternal–fetal medicine (MFM) system of care in order to achieve the required improvement in maternal and fetal health.

The first 9 months of life shapes the offspring’s adulthood while simultaneously impacting maternal life after pregnancy.

Such long-term effects on the health of mothers and their children are mediated through epigenetic, physiological, endocrinological, and biochemical pathways and by imprinting of responses to stress. They contribute to the increased postpregnancy risk of developing noncommunicable diseases (NCDs) that are passed on from one generation to the next through the critical period of pregnancy. A need for an all-encompassing approach for improving maternal and fetal medicine is thus required to interrupt the vicious cycle that starts at pregnancy disorder in order to improve the maternal life in this generation and the fetal life of the future generations. The holistic approach is needed to merge the importance of maternal and fetal health in the MFM subspecialty. This chapter presents a new three-floor holistic and multidisciplinary model for maternal and fetal medicine. The model’s first floor is prepregnancy care and involves family planning and assessment of the prior risks for NCDs and their prepregnancy control and prevention. It continues through the introduction of the inverted pyramid of antenatal care that shifts the emphasis from the third to the first trimester of pregnancy, offering a multidisciplinary screening and risk assessment followed by individually tailored prevention and management pathways. The third floor is the postpregnancy health management to minimize long-term damage. This model of MFM care is proposed to improve maternal outcome and prevent short- and long-term complications not only to the mothers but also to their children and the coming generations.

Bringing maternal–fetal medicine to the new era of medicine

MFM was established a few decades ago as a multidisciplinary subspecialty dedicated to optimizing pregnancy and perinatal outcomes. The MFM subspecialty emerged from the need to combine diagnosis and treatment of both

the mother and her fetus in cases of high-risk pregnancies. The rapid advance in sonography, the introduction of MRI, and the leap jump of measuring fetal DNA in maternal blood have shifted the MFM emphasis to fetal medicine. This progress occurs in parallel to increased maternal morbidity and failures in the attempts to decrease maternal mortality rates over the last few decades.¹⁻³ Thus, there is a need to reemphasize the maternal component (M) in the MFM specialty by means of introducing new concepts and advanced diagnostic procedures and policies coupled with changes in education and training, in order to implement improvements in healthcare services for pregnant women and enable the introduction of a personalized medical approach.^{1,2}

In this commentary, we aim to present a new paradigm for healthcare service reorganization combining front-edge technologies for early diagnostics, prevention, and treatments that can assist healthcare organizations in achieving reduced morbidity and mortality while optimizing cost benefit for the obstetrical care as a whole and pregnancy outcomes in particular. The approach is patient centered and offers services to meet the individual patient needs.

The Neglected M in MFM

Although the maternal and fetal medicine subspecialty was originally introduced to equally address fetal and/or maternal aspects of pregnancy management, the main focus of MFM today is the diagnosis and treatment of fetal complications and improving neonatal outcome. The health of pregnant mothers is no longer getting sufficient attention. This situation may have been influenced by the rapid progress in prenatal diagnosis of congenital and chromosomal anomalies, the introduction of fetoscopic surgery for in utero treatments of fetal disorders and advanced imaging and Doppler methodologies, and the profound impact of these developments in reducing the incidence of major pregnancy disorders, stillbirth, and preterm birth.³

As the advanced treatment offered by neonatal intensive care units progressed, premature babies with very low birth weight are saved generating challenges for the postdelivery management of newborns.⁴

At the same time, maternal morbidity rates have been rising.⁵ One major contributor, mainly in developed countries, is the obesity epidemic⁶ causing increased rates of metabolic disorders, diabetes, hypertensive disorders, and cardiovascular diseases (CVDs), all of which are chronic in nature, in the general population. Women affected by these diseases have an elevated risk for pregnancy disorders, including hypertension disorders in pregnancy, gestational diabetes (GDM), and prematurity as suggested by the American College of Obstetricians and Gynecologists (<http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Obesity-in-Pregnancy>). The constant rise in the rates of delivery by cesarean section entails elevated risks of placenta accreta and hemorrhages.⁷ Furthermore, new assisted reproductive technologies opened the possibility for women to conceive among those with kidney, lung, heart, and other serious medical diseases

and for pregnancy at an advanced maternal age.⁸ Finally, there is a continuing trend across the developed world to postpone family planning and attempt to conceive at an advanced maternal age, with Italy leading the convoy with 34.9% of women delivering at age 35 and older as reported by the EUROPRESTAT project evaluating pregnancy statistics of 39 countries in Europe (<http://www.europeristat.com/reports/european-perinatal-health-report-2010.htm>). While this may in turn be a source of organ regeneration and extension of maternal longevity,⁹ it is also associated with increased risk for preeclampsia, intra uterine growth restriction (IUGR), and preterm birth.¹⁰ Consequently, a higher percentage of pregnant women are at high risk for developing serious maternal complications during pregnancy and the postpartum period.^{1,5}

In the United States, the major etiologies of maternal mortality during pregnancy, labor, and delivery are CVDs, 14.6%; infection or sepsis, 13.6%; non-CVDs, 12.7%; cardiomyopathy, 11.8%; hemorrhage, 11.4%; thrombotic pulmonary embolism, 9.6%; hypertensive disorders of pregnancy, 9.4%; cerebrovascular accidents, 6.2%; amniotic fluid embolism, 5.3%; and anesthesia complications, 0.7% as reported by the National Center for Chronic Disease Prevention and Health promotion, NCCDPHP (<http://www.cdc.gov/reproductivehealth/MaternalInfantHealth/PMSS.html>). These leading causes of maternal morbidity and mortality demonstrate that prepregnancy health (especially in the context of CVDs) contributes to increased pregnancy complications. Further emphasis of the potential benefit of early diagnosis and prevention (especially of hypertensive disorders during pregnancy) is attempted at reducing maternal mortality during pregnancy or immediately after delivery, also demonstrating how the mode of delivery and postnatal care impacts pregnancy outcome.^{9,10}

In the 2010 annual convention of the American Society for Maternal and Fetal Medicine, M.E. D'Alton was the first to address the question: "Where is the 'M' in Maternal Fetal Medicine?"¹¹ She urged to outline a specific plan for clinical, educational, and research initiatives in order to return the maternal "M" in MFM to the center of fetal and maternal medical care. In 2012, a step forward was undertaken by the leading U.S. authorities in obstetrics and gynecology by publishing their recommendations to enhance education and training in maternal care for MFM fellows, to improve medical care and management of pregnant women, and to address critical research gaps in maternal medicine.^{4,11} However, to really return the focus to the maternal M in MFM, education and training alone are insufficient. A revolution in service provision and introduction of the front-edge diagnostic and prevention technologies is required in order to shift the emphasis to early diagnosis and prevention, to introduce an individualized approach, to combine the front-edge genomics into the standard of care, and to shift the paradigms of perinatal and antenatal care to emphasize maternal and not just fetal aspects. And this will make the difference, save lives, and improve the use of financial resources to the patients' benefit. Such a paradigm shift is timely and is required to improve maternal health and fetal outcome.

This paradigm shift involves the introduction of multidisciplinary assessment procedures and novel test technologies with a focus on early diagnosis and prevention/management of the major causes of maternal morbidities and mortality.¹² In this commentary, we suggest the introduction of the inverted pyramid of antenatal care for early (first trimester) screening of a pregnant woman. The aim is to detect the development of pregnancy disorders and outline the personalized pathway for the prevention of these disorders to improve pregnancy outcomes, as proposed by Nicolaides.¹³ It is proposed to implement the inverted pyramid of prenatal care as the major paradigm for antenatal care during pregnancy.

Additional components offered in the current commentary is the introduction of new means and tools for implementation into the routine practice of pregnancy management the methods for *prepregnancy* family planning and health evaluation. It will enable to assess the prior risks before conceiving and to plan ahead and provide appropriate maternal care facilities. Using this framework will allow prior risk assessment and management before entering into the process of conceiving.

Offering postpregnancy prevention and management can then complete the whole framework of comprehensive services for pregnant women.

Combining the progress in fetal medicine with innovation in maternal health not only offers remerging the M and the F of the MFM specialty but will also bridge the discrepancies and introduce new strategies for pregnancy management. This approach can assist healthcare organizations in optimizing obstetrics care and pregnancy outcome.¹⁴

Bridging between maternal and fetal medicine: The maternal–fetal medicine hypotheses

The integration between the “M” and “F” components of maternal and fetal medicine is required to enable comprehensive care and management.¹² During pregnancy, women’s bodies and their fetuses are interconnected. Maternal heart adjustments occur in response to the increased physiological burden of pregnancy and the signaling of circulating factors that are exchanged between the mother and the fetus having a positive/negative impact.¹⁴ These are just obvious elements of the required integrative whole framework of the “M” and “F” components of MFM.

Pregnancy shapes adulthood health: The Barker hypothesis (fetal origins of adult diseases: programming and imprinting in utero)

Low birth weight: Increased risk for lifelong CVD and diabetes Barker was the first to demonstrate how low birth weight is associated with elevated risk for CVDs in adulthood.¹² He postulated that fetal shortage of nutrients and oxygen due to placental insufficiency is associated with fetal development of physiological pathways for stress adjustment underlying recruitment of the same pathways in adulthood, and leading to the development of higher adulthood susceptibility to obesity, diabetes mellitus (DM), hypertension, and CVDs. According to Barker,

these “programmed changes” are metabolic adaptations to fetal undernutrition expressed in enhanced catabolism and self-consumption of substrates for energy supplies.¹⁵ A prolonged fetal adjustment period to undernutrition also reduces endocrine concentration of fetal growth hormones, via the reduced transfer of amino acids and glucose across the placenta, due to decreased maternal insulin-like growth factor. These changes are followed by reduced rates of fetal growth also creating a process of response to stress that is repeated in adulthood life and thereby lead to metabolic disorders and CVDs.¹⁶

Low birth weight was shown to be associated with increased rate of ischemic heart diseases in adulthood. Studies with three large cohorts (>16,000 individuals) in the United Kingdom have shown that mortality from ischemic heart disease later in life were twofold higher in those born <2.5 kg at birth compared to the ones born >4.3 kg.¹⁷ Thin or stunted and small trunk babies who were born due to in utero undernutrition, hypoxia, and other changes are predisposed to consequential diseases in the long term.¹⁸ Furthermore, increased mortality rates from coronary heart diseases are found among men born with a low birth weight, low placental weight, or narrow head circumference.¹⁹

The prevalence of Diabetes Mellitus type 2 (type 2 DM) and impaired glucose tolerance later in life are threefold higher in people who were born with the smallest (<2.5 kg) birth weight compared to the people who weighed >4.3 kg at birth.^{20,21} There is evidence that deficiency in insulin production and insulin resistance are both determined in utero and that low-birth-weight babies develop in utero the “insulin resistance syndrome” that prevailed in their adulthood, causing an impaired glucose tolerance, hypertension, and high concentrations of triacylglycerol.^{21,22}

The extreme example of the long-term impact of nutrient shortage in pregnancy was discovered with the Dutch study of individuals who were in utero during the Dutch famine of 1944–1945.²³ This study provides evidence linking fetal undernutrition to programmed insulin resistance and type 2 diabetes. Their glucose tolerance tests at age 50 years were all higher than in those conceived before or after the famine.^{21,22} This study has also provided evidence for long-lasting epigenetic effects transferred from the newborn to their progenies, not through the mother but through the father, indicating the profound impact of undernutrition on the DNA methylation of germ cells associated with facilitated aging-related diseases for the generations to come.^{16,21} *Another example is the Chinese famine during 1954–1964, which was identified to be associated with a higher likelihood to develop metabolic syndrome in adulthood.*²⁴ Based on all these changes, *Time* magazine published its series of articles on the way the first 9 months shape the person’s health throughout life (<http://content.time.com/time/magazine/article/0,9171,2021065,00.html#ixzz2s8IDDoru>).

Blood pressure and hypertension A multitude of studies have found a trend in which each 1 kg increase in birth weight is associated with a fall of around 3.5 mmHg in blood pressure in adult life.²⁵ There is a strong association between

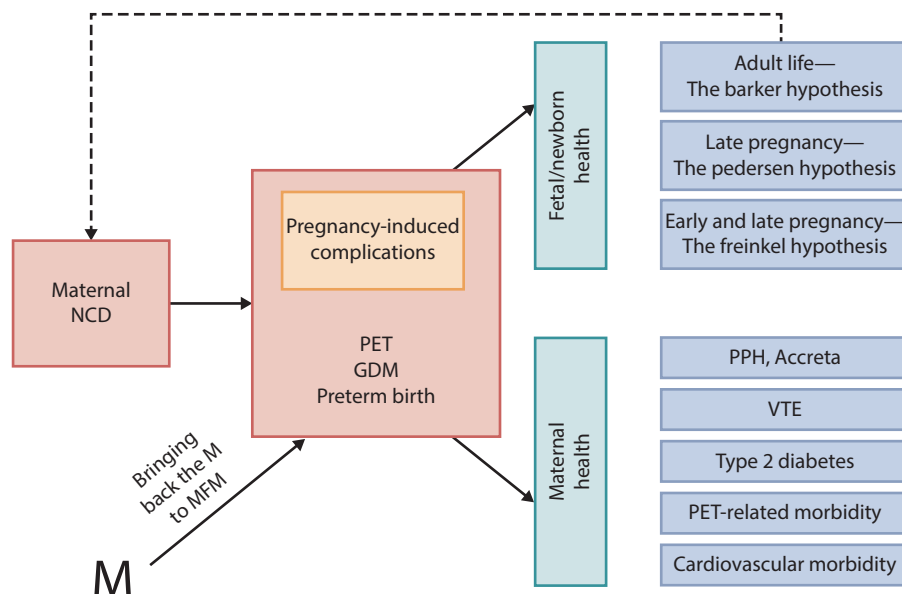


Figure 1.1 Maternal medicine meets fetal medicine; the vicious cycle—noncommunicable disease epidemic.

hypertension disorder in adulthood to low birth weight, thinness, stunting, and below-average head circumference.²⁶

All the aforementioned examples have demonstrated how birth weight, in utero conditions, and epigenetic changes are associated with the increased adulthood morbidity from NCDs leading to a vicious cycle for generations to come.

Maternal aspects of placenta insufficiency

Increased maternal CVDs and decreased life expectancy due to preeclampsia Another consequence of placental insufficiency is preeclampsia, particularly the early form of the disorder. McDonald et al., in their meta-analysis of 35,000 women, have shown that hypertension disorders in pregnancy are associated with increased maternal morbidity from CVDs and DM 10 years later.²⁶ Furthermore, Irgens et al., using the Medical Birth Registry of Norway, have shown in >600,000 women and their spouses a 10-year shortening of maternal longevity following early preeclampsia and IUGR.²⁷

Thus, placental insufficiency is programming high susceptibility to CVDs and diabetes not only among babies born with lower birth weight but also among their mothers.

NCDs and maternal morbidity

Prepregnancy conditions of maternal health (obesity, diabetes, anemia, and undernutrition, kidney, blood, and heart diseases) all impact maternal health during pregnancy.²⁸ Prepregnancy diabetes and GDM can cause macrosomia, obstructed labor, postpartum hemorrhage, and neonatal mortality due to prematurity, respiratory distress syndrome, hypoglycemia, etc. Maternal undernutrition can lead to fetal metabolic and hormonal alterations causing lifelong susceptibility to certain diseases. At the same time, low birth weight and accelerated growth during childhood have been demonstrated as risk factors for CVD and type 2 DM.

This vicious cycle starting from prepregnancy health, influencing the outcome, which in turn causes adulthood

diseases associated with pregnancy disorders in the next generation onward, is now recognized as the link between the origin of NCDs in neonatal life and adulthood diseases (Figure 1.1). It requires implementation of healthcare assessment and preventive interventions before pregnancy to reduce infant and maternal morbidity and mortality and prevent developing NCDs later in life.²⁹

Vicious cycle of the NCD epidemic (obesity, diabetes, hypertension, metabolic syndrome): Fetal programming

According to the World Health Organization (WHO), of the 57 million people who died in 2008, 36 million died from NCDs, stating that NCDs represent a “slow motion disaster.”³⁰ The four main chronic diseases responsible for most NCD deaths are CVDs, including heart attacks and stroke (17.3 million annually); cancer (7.6 million); respiratory diseases, such as chronic obstructive pulmonary disease and asthma (4.2 million); and diabetes (1.3 million).³¹

Intermediate risk factors predisposing to NCDs include hypertension, elevated blood glucose, hyperlipidemia, overweight, and obesity, which all can lead to the development of CVDs.

The hypothesis about the developmental origins of health and disease put forward the concept that internal and external environmental conditions during pregnancy cause critical biochemical, endocrinological, and epigenetic modifications in the DNA, cell differentiation, and formation of specific tissues in both the mother and her fetus/newborn.³¹ While at birth these functional changes are currently not detected by conventional tests and are likely to be initially masked by systemic effects, the slow process of their development into disorders may impact the health of the mothers and their children later in life.³²

Epigenetic changes in DNA methylation and Cytosine-Phosphate-Guanidine (CPG) Islands cause the silencing or activation of certain genes that are essential for the

physiological function in early childhood and in adult life and could lead to an accelerated DNA clocking and aging.³³ Thus, epigenetic methods could shed light on in utero processes that predispose individuals to diseases in adult life.^{31–33}

The programmed in utero changes of the metabolism and physiology could lead to dysfunction and disease in adulthood. As such, the related pregnancy disorders such as preterm delivery, IUGR, and preeclampsia can be considered as markers of increased risk of CVDs, obesity, and metabolic disorders, and GDM could be the source for obesity and DM or—overall—the origin of NCDs. In fact, the American Heart Association (AHA) has identified women who develop hypertension disorder during pregnancy and women who have GDM as the two new high-risk groups for developing CVDs, which require special management and monitoring as included in the American Heart Association Stroke Council guidelines for the prevention of stroke in women (<http://blog.heart.org/preeclampsia-doubles-womens-stroke-risk-quadruples-later-high-blood-pressure-risk/>).

In order to reduce the influence of epigenetic, biochemical, endocrinological, and physiological preconditioning of NCDs in the perinatal period, preventative measures should be introduced, including the provision of sufficient prenatal care; prevention or optimal treatment of conditions such as obesity, diabetes, and chronic hypertension; and also directing the attention at prepregnancy assessment of their prior risks and family planning to assure women begin their pregnancy period with rich metabolic reservoirs and with a pre-planned program for their pregnancy management based on their prior risks.

In this way, it may be possible to inhibit negative epigenetic, biochemical, physiological, and endocrinological programming. The importance of good maternal care beginning prior to conception and continuing during pregnancy and after delivery is therefore crucial to shape the health of mothers and their babies for life and to prevent the impact of internal and external effects of long-lasting changes, thus reducing the likelihood of NCD development in adulthood.

Reconnecting the M to the F in MFM

The importance of improving maternal healthcare and services can leverage on recent achievements of the medical research to introduce a strategic plan and policy.

A healthy pregnancy begins before conception.^{34,365} It continues during the gravid period with early recognition and management of complications if they arise, with strategies to prevent complications, planning for a timed delivery, and follow-up in the postdelivery period.³⁷ Healthcare providers can help women prepare for pregnancy and for any potential problems during pregnancy with postpregnancy management of complications that were not previously prevented.³⁷

The Maternal Medicine Meets Fetal Medicine project of the Clalit Health Services proposes a new strategy and aims to establish a new paradigm of pregnancy care. It extended from prepregnancy evaluation of prior risk of developing NCDs^{34,35} to the emphasis on a thorough evaluation of the risk

of developing pregnancy disorders in the early trimester of pregnancy³⁶ and the development of individualized pregnancy management and disorder prevention and monitoring toward a timed delivery,³⁸ including management of maternal and newborn health for those who developed pregnancy disorders.³⁷

The model proposes a change in the organization of the clinical services to pregnant women as a combination of hospital-based clinics and community clinics. This combined paradigm of evaluation, prevention, treatment, and follow-up could provide high-quality perinatology services from prepregnancy planning, through antenatal follow-up, to labor and to delivery and through the postpartum management.

Clalit Health Services approach

Clalit Healthcare Services is the largest health management organization (HMO) in Israel and one of the largest in the world. It has more than 4 million insurees, operating more than 100 community clinics, 40 regional women's health centers, and 14 hospitals with some of the leading maternal–fetal medicine departments in Israel. The HMO employs thousands of family physicians and gynecologists, trains hundreds of interns and fellows, involves thousands of nurses and many midwives, and manages advanced laboratory services and testing infrastructure.

As a leading HMO in Israel, the organization is in the process of implementing the Clalit's Maternal Medicine Meet Fetal Medicine project that is built of three “floors”:

Pre-Pregnancy: Identifying NCDs and carriers of gene disorders before pregnancy

The goal of the first floor is to improve maternal health and prenatal outcome *before* the women get pregnant. While part of this campaign involves promotion of health education to families, it also involves the assessment of the prior risk of developing pregnancy disorders and offers appropriate interventions with proven efficacy.^{38,39}

In 2013, the AHA introduced the seven metrics to establish three health levels of well, intermediate, and sick status, based on blood pressure, obesity, blood glucose and cholesterol levels, smoking, physical activity, and healthy diets, adjusted to age and gender. The seven metrics are linked through a comprehensive algorithm to divide patients into one of the three categories.⁴⁰

Preconception evaluation should follow this approach to establish the high, intermediate, and low risk of developing pregnancy disorders, given that the same criteria that are considered as risks for hypertension disorders in pregnancy, GDM, spontaneous preterm birth (SPB), and fetal growth restriction are underlying risks for developing major CVDs and metabolic disorders.^{30,31,41}

Thus, three categories of risk levels in pregnancy will be defined, and stratification will be performed at prepregnancy visit(s) to the family physician. Using patient interviews and blood tests (including the hemoglobin A1C test) and obtaining family, pregnancy, and medical history from the patients and from their electronic medical record, the family physician will gather all the information available to establish

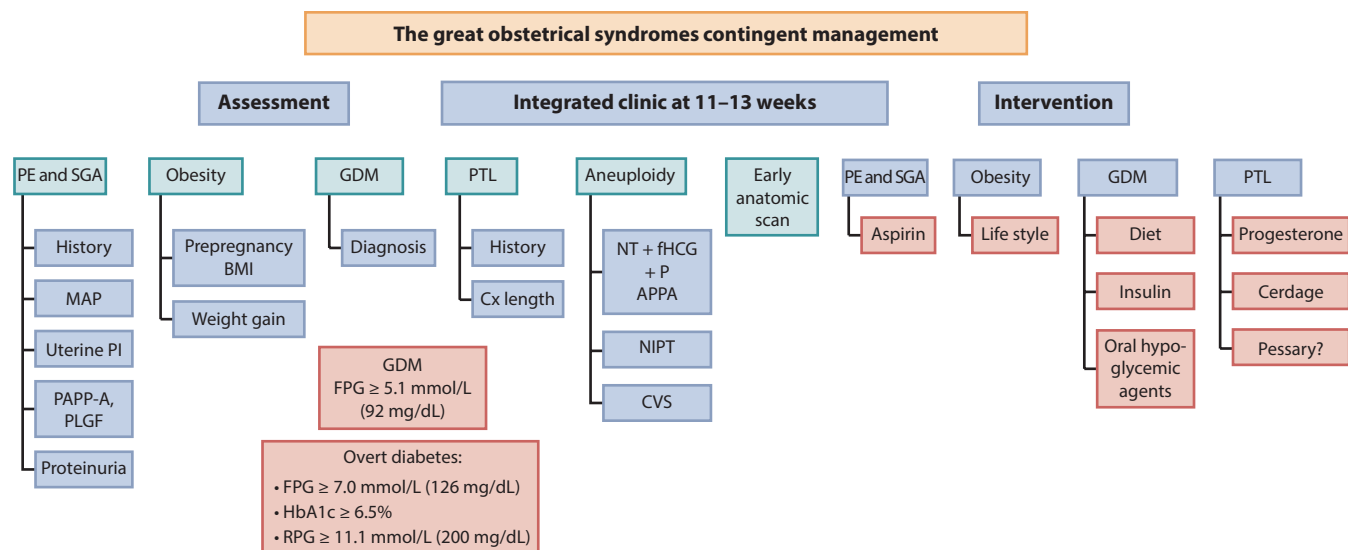


Figure 1.2 The first trimester clinic and contingent management.

the prepregnancy risk for NCDs. Hadar et al.⁴² have demonstrated that when glycemic control and obesity are optimized prior to gestation, smoking and drinking are avoided before pregnancy, and moderate physical activity and a healthy diet are adopted before conception—which could prevent GDM, congenital malformation, abortion, prenatal and neonatal death, and adverse pregnancy outcomes.⁴²

The whole system will be accompanied by a team of genetic counselors in order to assess the prior risk of major genetic disorders. This approach was adopted by American College of Obstetricians and Gynecologists (ACOG) antenatal Care—Introducing the Inverted Pyramid for Pregnancy Management⁴³ and is widely offered in Israel. Chips for blood test are available for all couples to identify carriers of major ethnic-associated DNA-based diseases. Couples identified as carriers will be directed for genetic counseling to consider various assisted fertility technologies, including preimplantation Genetics diagnosis (PGD), whereas others are advised to begin with spontaneous conception.

For assessment of the major NCDs, the family physician/community gynecologist could prepare the prior risk evaluation and direct women to either dietitians and even to physical trainers to improve her prepregnancy conditions if she is at intermediate risk, or to an MFM specialist for glycemic controls and other endocrinological and biochemical monitoring, if her prior risk is high. Those at a low risk are reassured and could start with their family planning.

The success of this preconception level of care depends on the implementation of unified guidelines within the entire complex of family physicians and obstetricians in the community, together with dietitians, physical trainers, and high-risk hospital clinics.⁴² They will have joint meetings to discuss cases and guidelines and will use unified medical records that will create a database for future quality evaluation and research. As already reviewed by Hadar et al.,⁴² the effectiveness of prepregnancy care is highly dependent on such guidelines, education, and training, including patient education.⁴⁴

Inverted pyramid of antenatal care and personalized risk management

The second floor of Clalit's Maternal Medicine Meets Fetal Medicine project is proposed to follow the inverted pyramid of antenatal care suggested by Nicolaides.¹³ Unlike the current antenatal care that focuses on a uniform service model reacting to complications when they develop and focusing on a uniform high-frequency visit plan during the third trimester of pregnancy, the inverted pyramid of antenatal care focuses on a thorough first trimester risk evaluation and aims to implement a personalized approach for subsequent management according to the individual risk score (Figure 1.2).

The approach applies to both those who are already managed by the MFM specialized center due to prior risk and to the rest of the pregnant women population.

The first prenatal visit aims to quantify the woman's risk in this pregnancy in developing major pregnancy disorders. The evaluation is based on the obstetrics and medical history, demographics, biochemical serum markers, and biophysical parameters, including mean arterial blood pressure and sonographic image of nuchal translucency and uterine artery Doppler pulsatility index. All are entered into the risk algorithms to provide the patient risk for any of the chromosomal aberrations, preeclampsia, and IUGR, SPB, and GDM.

If performed at the community level, the inverted pyramid of antenatal care requires training and certification of the community ob-gyn physicians to incorporate the wider range of testing methodologies and equipment for providing a multiple marker screening and the use of advanced risk algorithms to enable the assessment of the patient risk to a diversity of major pregnancy disorders. In the United Kingdom, this stage is carried out in hospital departments that specialized in these procedures.

Based on the specific pregnant woman's medical and obstetric history, her serum markers, blood pressure, and sonographic examination, the risk score will be determined.

Accordingly, her pregnancy management will be adjusted by a contingency management algorithm that will issue an individualized pregnancy monitoring tailored for low-, intermediate- and high-risk patients.

While women at high risk are directed toward more frequent visits and offered preventive care to prohibit/reduce the risk of developing particular disorders while allowing the majority of gravid women who are at low risk to enjoy less medically intense pregnancy care, many women wish to experience pregnancy as a healthy period.

The smaller group of women who are at a higher likelihood of developing the threatening outcome will then be directed to an intensive process of evaluation and, when appropriate, offered preventive treatment. The smaller size of this group enables to focus the efforts on those who need it, while the majority will not require intensive medical attention.

The model is shifting perinatal management from the treatment of complications after they develop to early risk identification during the first trimester of pregnancy to enable prevention. For example, women who are at an elevated risk for major pregnancy disorders, such as placental insufficiency, are offered the use of daily aspirin already in the first trimester to prevent the development of preeclampsia and IUGR, based on evidence that low-dose aspirin from the first trimester prevents preeclampsia, fetal growth restriction, and stillbirth by at least 50%.⁴⁴ It has been evaluated that the cost of implementing such broad first trimester evaluation and prevention is much cheaper than treating the long-term impact of preeclampsia on mothers and their offspring, preventing further mortality and morbidity.⁴⁵ This approach was already taken in Australia on a small group of patients, which is further evaluated with the European Commission (EC) project Aspirin for preeclampsia (ASPRE). The vast majority of women in the very-low-risk category can be reassured that preeclampsia and IUGR are unlikely.

The power of the inverted pyramid and of the proposed contingent model of prevention could be demonstrated for the case of Down syndrome. Early screening is based on maternal age, biochemical markers, and nuchal translucency. Based on the initial risk, a small proportion of women at the highest risk are directed to interventional procedures (Chorionic Villus Sampling [CVS], or early amniocentesis) and karyotyping. The intermediate-risk group is referred to cell-free fetal DNA testing to assess for chromosomal abnormalities while the very-low-risk group is sent home. With this approach, the fetal medicine foundation group was able to show prediction of more than 97% of all major trisomies in the first trimester.⁴⁶

In the case of SPB, an algorithm at 11–13 weeks identifies a small, very-high-risk group with a history of SPB and a short cervix that can benefit from the treatment of cerclage or followed up closely and offered prevention treatment with progesterone at the 22nd gestational week. Based on randomized studies, evidence was found that the use of progesterone can prevent SPB by 45%.⁴⁷ The vast majority of women in the very-low-risk category can be reassured that SPB is unlikely.

Similar contingent approaches are being developed for GDM and macrosomia.⁴⁸ Metformin and insulin have been shown to prevent GDM and macrosomia by 30%–40%.⁴⁹

In the Clalit version of the inverted pyramid, low-risk pregnancies will be managed in community clinics, by general treating gynecologists. For high- and intermediate-risk pregnancies, follow-up will be offered via two potential pathways:

- *Hospital maternal–fetal medicine clinics:* High-risk pregnancy with a multidisciplinary team including specialized perinatologists, ultrasound experts and technicians, pregnancy nurse educators, dietitians, genetic counselor, and perinatal laboratory personnel with immediate referral to invasive diagnostic tests.
- *Women's healthcare centers:* A regional network of clinics that will have a dedicated service for high-risk women, with specialized perinatologists working in tight cooperation with the regional obstetric department. It is important to note that in Israel today, some tests that are in the market and are important for a complete risk assessment as offered by high-risk algorithms developed by the Fetal Medicine Foundation in London are not yet included in the pregnancy tests covered by the state insurance policy for pregnant women.* Thus Clalit offers a local additional alternative, through its fully owned complementary insurance network of Mor for Women Health providing access to these new services. The inverted pyramid of antenatal care proposes two major additional clinic visits in the second trimester, at the 22nd and 32nd gestational weeks. The model suggests a stepwise reduction in the number of patients at the high-risk group during these additional visits, and the identification of the intermediate group, which can be removed from close surveillance. Those that are identified to develop these conditions in late pregnancy can be offered planning for a timed or early delivery.

Postpregnancy: Early prevention of NCDs by early examination shortly after birth

The third floor of Clalit's Maternal Medicine Meets Fetal Medicine project is offered for the postpregnancy period (Figure 1.3). The prevalence of various forms of NCDs—the whole spectrum of metabolic syndrome and premature CVDs—is increased in women with a history of maternal placental syndromes (pregnancy-induced complications), including GDM, pregnancy-associated hypertensive disorders (e.g., preeclampsia), fetal growth restriction, preterm labor, and placental abruption.⁵⁰ Following pregnancies with any of the aforementioned conditions, the information will be passed to the family physician, neonatologist, and pediatrician, which will refer the patients to the needed consultants—e.g., diabetologists, endocrinologists,

* In this context, it is important to note that this community clinic-based solution should be adopted as the healthcare model of each country that should involve not just midwives but also obstetric gynecologists.

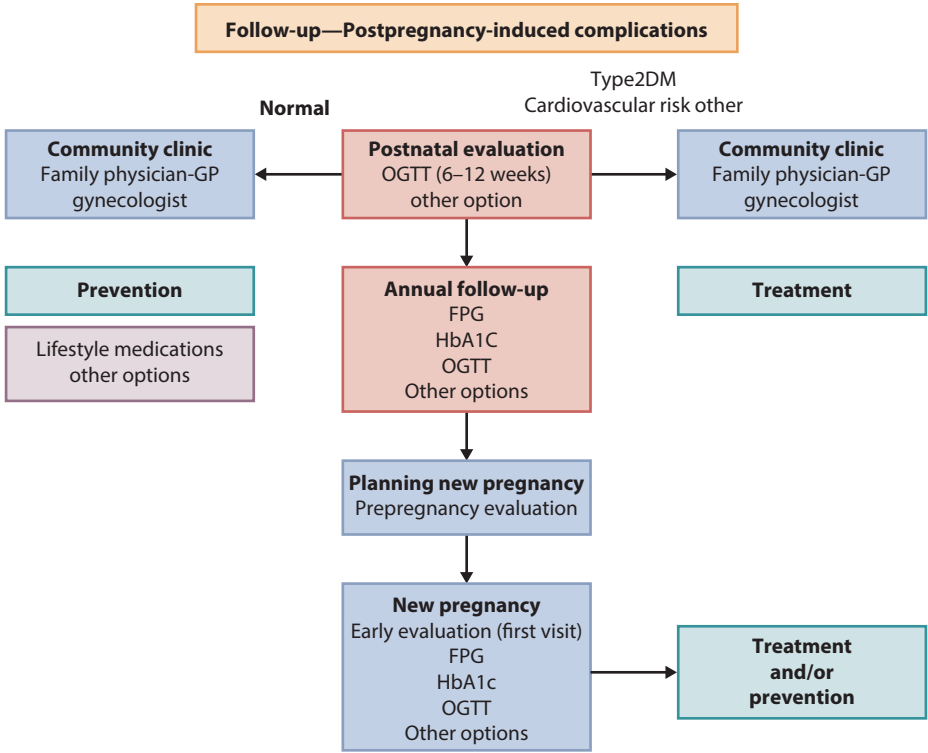


Figure 1.3 The postpregnancy clinic.

cardiologists, and nutritionists. Thus, the women will be immediately managed aggressively in community clinics that will provide measures for the prediction and prevention of future pathological conditions, including lifestyle management, medication, and family lifestyle advice and support.

Summary

NCDs such as CVDs, diabetes, obesity, and hypertension have significant adverse impacts on maternal health and pregnancy outcomes, and through the imprinting mechanism of intrauterine programming, the burden of future NCDs is highly influenced by pregnancy disorders and impacts the burden of NCDs in future generations.^{51,52}

Research today has shown repeated cycles of vulnerability to NCDs through major pregnancy disorders such as low birth weight, preeclampsia, GDM, and SPB that are propagating the risk for NCDs to subsequent generations through epigenetic, physiological, endocrinological, and biochemical pathways.

Clalit's Maternal Medicine Meets Fetal Medicine project is based on three "floors." At the core is the inverted pyramid of antenatal care that offers a systematic method to screen and prevent pregnancy disorders according to the principles set up by Nicolaides,¹³ involving first trimester risk score and contingency managements of low-, intermediate-, and high-risk pregnancies according to individualized management plans. In the preconception period, Clalit's Maternal Medicine Meets Fetal Medicine project offers an additional floor to

evaluate the preconception risks to adjust patient's glycemic control and dietary, physical activity, and nonsmoking habits before conception. Combining the two floors will improve pre- and postpregnancy management and integrate the skills of the specialists in maternal and fetal medicine with internal medicine and family physicians to substantially improve maternal and fetal outcome. The preconception service meets the needs and habits of the young generation through communication and family planning. The inverted pyramid floor forms the opportunity for the majority of pregnant women to experience pregnancy as a healthy period, offering them reassuring evidence to enjoy such an approach. The small proportion of women who are at a high risk and need close surveillance and perhaps treatment will have the opportunity to do so and will be offered a sensible service personalized to their needs. Together the two floors are tailored better to the public. The dedicated postpartum and child development floor could offer better monitoring to women who experienced pregnancy complications in adjusting their lifestyle and taking healthcare measures. It enables early intervention and diagnosis of newborn complications to reach sufficient nutrient support, physical training, physiotherapy, and cognitive progress in a period of plasticity of the brain and of other tissues to achieve better outcomes.^{51,52}

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2 History of diabetic pregnancy

David R. Hadden

Introduction

One hundred years ago, the medical literature on diabetic pregnancy was very limited. Pregnancy itself was no less frequent, but the outcome was affected by so many other major problems that the influence of a medical disorder of a chronic nature was both unrecognized and disregarded. Diabetes mellitus was also less prevalent, due both to demographic differences in the age of the population and to epidemiological factors—mainly the absence of any effective treatment so that young people with diabetes had a life expectancy of only a few years. The diagnosis of diabetes depended on the demonstration of sugar in the urine and the well-known symptoms of thirst, polyuria, and weight loss, but there was no accurate measurement to assess severity, and the distinction between what are now known as type 1 and type 2 diabetes was only anecdotal. There was no documentation of the specific long-term complications of hyperglycemia in the eyes, nerves, heart, kidneys, or blood vessels.

Early history of diabetes

Diabetes was well recognized as a medical disorder >2000 years ago, and some well-known references are worth quoting. The ancient Egyptian Ebers papyrus, dating to 1500 BC, records abnormal polyuria; the Greek father of medicine Hippocrates (466–377 BC) mentioned “making water too often” and Aristotle also referred to “wasting of the body.” Aretaeus of Cappadocia (AD 30–90) in Asia Minor (now Turkey) is credited as the first to use the name “diabetes,” which is Greek for a siphon, meaning water passing through the body: “diabetes is a wasting of the flesh and limbs into urine – the nature of the disease is chronic, but the patient is short lived ... thirst unquenchable, the mouth parched and the body dry” The famous Arabian physician Avicenna (AD 980–1027) recorded further important observations that maintained and extended the previous Greek knowledge through what became known in Europe as the Dark Ages: he described the irregular appetite, mental exhaustion, loss of sexual function, carbuncles, and other complications. There are also references to diabetes in ancient Hindu texts (AD 500) as a “disease of the rich, brought about by gluttony or over-indulgence in flour and

sugar,” and in early Chinese and Japanese writings “the urine of diabetics was very large in amount and so sweet that it attracted dogs.”^{1,2}

After the European Renaissance, the first physician to rediscover and record the sweetness of the urine in diabetes was Thomas Willis in London (1679): “The diabetes or pissing evil ... in our age given to good fellowship and guzzling down of unalloyed wine.” And Mathew Dobson 100 years later in Liverpool first demonstrated chemically the presence of sugar in the urine of diabetic patients. The demonstration by Oskar Minkowski (1889) that removal of the pancreas in a dog unexpectedly resulted in uncontrolled polyuria—the urine sugar attracted flies in the laboratory to the puddles on the floor—was the significant observation that eventually led to the extraction of insulin from the pancreatic islets in Toronto in 1922.³ The story of the discovery of insulin is a remarkable record of disappointment: it was almost discovered in 1906 by Zuelzer in Berlin, and then in 1912 by Scott in Chicago, but was actually extracted by Paulesco in Romania in 1920. However, the world recognizes the story of the Toronto group—including Banting, Best, Collip, and Macleod—as the definitive discovery, and in 1923, the Nobel Prize in Physiology or Medicine was awarded to two of them, Frederick Banting and JJR Macleod.⁴

Up until then, the only effective treatment for diabetes had been dietary, and it was well known that restriction of food would ameliorate the symptoms. John Rollo had demonstrated this with his patient Captain Meredith in the army in Ireland in 1797, who obeyed his doctor’s advice, documented the reduction in urine volume and subsequent weight loss, and even extracted sugar from the urine by evaporation. The dietary approach was carried to its logical extreme by the overenthusiastic approach of FM Allen in New York (1919), whose starvation therapy often temporarily returned the blood glucose to normal, but only succeeded in extending life for a year or so in the severe juvenile cases, all of whom became skeletally thin. Dr. Elliott Joslin is remembered as the Boston physician who bridged the period immediately before insulin’s discovery and the exciting clinical demonstration of its effectiveness in the following decade.⁵ In London, Dr. Robin Lawrence, diabetic himself, on dietary therapy only in his early twenties, recorded how his life was saved in 1923 by a telegram from his doctor in Kings College Hospital: “I’ve got insulin, and it works – come back quick.”

He survived for many years and became the leading diabetes specialist in England.⁶

These two doctors, Joslin in Boston and Lawrence in London, became the leaders of the revolution that would take place in both the opportunity for and the outcome of pregnancy in diabetic women.

Pregnancy and diabetes before the discovery of insulin

A full historical review of fertility and of the outcome of pregnancy in different parts of the world is beyond the scope of this chapter, but there are a number of aspects that are of particular relevance to the story of diabetes. Medical history in particular is constrained by publication bias, and there is much more available data regarding Europe and North America than in other parts of the world. The geographical and ethnic differences in the distribution, development, and management of diabetes in different places at different times would be of great interest to review, but as the data are patchy and both diabetic and obstetric treatments often poorly defined, it may be that “History followed different courses for different peoples, because of differences among peoples’ environments, not because of biological differences among peoples themselves.”⁷ There are certainly both environmental and genetic reasons for the differing prevalence and incidence of diabetes in different countries, as much as for the different outcomes of pregnancy, but the international historical study of these factors is still in its infancy.

The collection of vital statistics first became available at varying times in the developed Western countries. The Scandinavian countries were first Sweden (1749) and Denmark (1801), England and Wales followed (1838), and then Russia (1867); although the process was initiated in the United States in 1880, it did not become complete until 1933.⁸ Fertility rates have varied as much as death rates and migration in different countries, so that population dynamics will have a considerable effect on reported statistics for a single condition such as diabetes in pregnancy. The classical Malthusian checks on death rate—disease, famine, and war—and the effects of celibacy and restraint on birth rate will have more effect on the overall outcome statistics of pregnancy in diabetic mothers than the diabetes itself. The general fertility rate for England and Wales was about 130 live births per 1000 women between the ages of 15 and 44 in 1840 but is now only half that rate. At present, the total fertility rate (average number of children born per woman) varies from 2.1 in Western Europe to 6.7 in West Africa.⁹ However, there is no doubt that untreated diabetes must have been virtually incompatible with successful pregnancy before about 1850. In 1856, Blott in Paris wrote that “True diabetes was inconsistent with conception,” and certainly the then short life expectancy of a young woman with what we now call type 1 diabetes before the discovery of insulin would support that statement. Recent speculation on the possible nutritional causes of the present-day epidemic of type 2 diabetes in older patients means that any data on diabetes

successfully treated by diet only (which was probably type 2, rather than type 1) are of considerable theoretical interest, but it is perhaps important that these cases were not often reported in the literature and may well have been missed due to not even testing the urine for sugar.

In the preinsulin days, and for some time after, death of the mother during or soon after pregnancy from uncontrolled diabetes was the major risk. But maternal mortality was high for many reasons unrelated to diabetes, and retrospective analysis of data from England and Wales between 1850 and 1937 shows that poor interventional obstetric care with increased risk of puerperal sepsis was more important than social or economic deprivation.¹⁰ The maternal mortality rates for Scandinavian countries were much lower, and it is now clear that this was due to better overall obstetric management in the prevention of sepsis; in the United States, maternal mortality between 1921 and 1924 was 6.8 per 1000 births, in England and Wales 3.9 per 1000 births, and in the Netherlands only 2.5 per 1000 births.⁸ These differences at national level have been widely discussed, but must be borne in mind when considering the isolated effect of maternal diabetes over those years.

Overall perinatal mortality (death of the fetus after 28 weeks or within 7 days of delivery) has shown a more consistent fall over the same period of time in all Western countries. Most of the decline was in postneonatal mortality related to the rising standards of living and nutrition but also to improved public health measures—broadly speaking, the predominant form of infant mortality in Western countries was postneonatal in the nineteenth century and neonatal in the twentieth. There was not a close link between neonatal and maternal mortality, but there were very considerable differences in each of these measures between countries at the time of discovery of insulin (Table 2.1). The overall infant mortality rates in Scandinavian countries were persistently lower than in England and Wales, or Belgium, between 1920 and 1965, although all countries show a steady exponential decline.⁸ As perinatal mortality is now used as

Table 2.1 Overall maternal mortality and infant and neonatal mortality for selected countries at the time of discovery of insulin

Country	Maternal deaths, 1921–1924, per 1000 births	Infant deaths, 1924, per 1000 births	Neonatal deaths, 1924, per 1000 births
The Netherlands	2.5	67.3	18.6
Japan	3.3	166.4	67.5
England/Wales	3.9	75.1	33.1
Australia	4.5	57.1	29.8
United States	6.8	70.8	38.6

Source: Loudon, I., *Death in Childbirth: An International Study of Maternal Care and Maternal Mortality 1800–1950*, Clarendon Press, Oxford, U.K., 1992, pp. 1–622.

a main comparator for the outcome of diabetic pregnancy, it is important to bear these long-standing historical trends in mind.

Congenital malformations are also an important comparator for obstetrical results, but the recognition of a possible link with maternal diabetes is much more recent: anecdotal accounts in small series in the 1940s were not supported until the report by the U.K. Medical Research Council in 1955¹¹ and the larger series from Copenhagen in 1964.¹² Historical records on the frequency of congenital malformations are very incomplete, and it was not until the International Clearinghouse for Birth Defects began to operate after 1974 that any baseline data on the prevalence of congenital malformations became possible.¹³ It is still difficult to compare results for specifically identified diabetic pregnancies with overall national malformation rates where the collection of cases is much less detailed.¹⁴ Other obstetrical complications such as preeclampsia appear today to be more common in diabetic pregnancy, but it is difficult to trace this possible interrelationship back to the days before organized antenatal care. Some of the cases where maternal death occurred in a diabetic pregnancy may have been due to eclampsia rather than diabetic coma.

Gestational diabetes

The concept of gestational diabetes, actually meaning hyperglycemia due to the pregnancy itself but in practice defined as “carbohydrate intolerance of varying severity with onset or first recognition during pregnancy,” is also recent.¹⁵ In the very first recorded case, Bennewitz, in 1823, considered that the diabetes was actually a symptom of the pregnancy, and as the symptoms and glycosuria disappeared after at least two successive pregnancies, he had some evidence to support his views.¹⁶ That lesser degrees of maternal hyperglycemia were also a risk to pregnancy outcome dates back to studies in the 1940s in the United States^{17,18} and Scotland,¹⁹ which showed increased perinatal mortality some years before the recognition of clinical diabetes mellitus. This led to the term prediabetes in pregnancy and to poorly defined concepts of temporary and latent diabetes. The first prospective study of carbohydrate metabolism in pregnancy was established in Boston in 1954, using a 50 g 1-hour screening test, which has subsequently been widely adopted in the United States.²⁰ O’Sullivan²¹ first used the name gestational diabetes in 1961, following the term metagestational diabetes used by Dr. JP Hoet in 1954 after his early studies in Louvain, Belgium.²² At that time, the U.S. emphasis was on establishing criteria for the 100 g oral glucose tolerance test in pregnancy as an index of the subsequent risk of the mother developing established diabetes, and the well-known O’Sullivan criteria were derived on this basis.²³ At about the same time, Mestman, in southern California, began to identify the very considerably increased perinatal mortality associated with abnormal oral glucose tolerance in the obstetric population of Los Angeles County Hospital, which then comprised >60% Latino mothers with the rest African-American and

only a few Caucasian.²⁴ Subsequent studies in many parts of the world have extended the recognition of what has now become, in some places, an epidemic of hyperglycemia in pregnancy. Jorgen Pedersen also used the term gestational diabetes in his monograph in 1967, but preferred to so classify a mother only after delivery, when he had demonstrated that her abnormal glucose tolerance in pregnancy had actually returned to normal postpartum; this rigorous definition has proved too difficult to achieve in practice.^{25,26} The true definition of hyperglycemia in pregnancy judged by the internationally acceptable 75 g oral glucose tolerance test awaits the results of the large Hyperglycemia and Adverse Pregnancy Outcome study.²⁷ The enthusiasm of the team at Northwestern University, Chicago, led by Norbert Freinkel and subsequently by Boyd Metzger has ensured that the concept of gestational diabetes is now firmly imprinted on the obstetric mind, as well as having established a major place as an epidemiological tool to study not only the immediate outcome of pregnancy but also the long-term effects on both mother and baby of the relatively short phase of hyperglycemia during the latter part of the pregnancy.

Important early publications

The historical development of understanding in obstetric, metabolic, and pediatric disciplines over the past 100 years is perhaps best illustrated by several more extensive quotations and commentaries on seminal papers from the early literature: Bennewitz HG, *Diabetes mellitus—A symptom of pregnancy* [translated from Latin].²⁸

This is the first reference to diabetes in pregnancy. Although the patient was young, the clearly described onset of her symptoms during the pregnancy would now classify this as gestational diabetes. Is it possible that she only survived because she has a milder case who responded to diet, while all the more severe type 1 diabetic patients died?

Henry Gottlieb Bennewitz publicly defended his thesis for the degree of doctor of medicine at the University of Berlin on June 24, 1824. It is a simple case report and review of the literature on the causes and treatments of diabetes known at that time. His Greek derivation of the word diabetes and his one-line definition of the symptoms are unchanged today: “Urine differing in quality and quantity from the normal ... accompanied by unquenchable thirst and eventual wasting.” Before giving the case history, he summarized his belief that the diabetic condition was in some way a symptom of the pregnancy, or due to the pregnancy. He noted that “Other disorders ... began to break out as the pregnancy matured ... the little fires which had hidden beneath the smouldering deceiving ashes broke forth and devoured again the woman’s condition in the most wretched manner.” He was convinced that “The disease appeared along with pregnancy, and at the very same time ...; when pregnancy appeared, it appeared; while pregnancy lasted, it lasted; it terminated soon after the pregnancy.” He showed a degree of humility when he remarked that his patient must be something of a rare bird.

The case history commences on November 13, 1823, when Frederica Pape, aged 22, was admitted at 7 months in her fifth pregnancy to the Berlin Infirmary. The first three pregnancies appear to have been unremarkable, but in the fourth in 1822 she had an onset of thirst and polyuria that had resolved spontaneously after delivery. These symptoms returned at an unspecified time in her fifth pregnancy: she had “a really unquenchable thirst—she consumed more than six Berlin measures of beer or spring water, although the quantity of urine greatly exceeded the amount of liquid consumed, and the urine itself smelt like stale beer. Her voice was weak, skin dry, face cold and she complained of a dragging pain in her back.”

Treatment was more a matter of belief than of understanding, but apart from having withdrawn 360 mL of venous blood all at once (the equivalent of 36 10 mL routine blood tests today) and taking a high-protein diet, probably deficient in vitamins, she must have benefited from the rest and care. The measurement of 2 oz of sugar in 16 lb (224 oz) of urine, which is equivalent to about 1% glycosuria, was Bennewitz’s only biochemical evidence of diabetes mellitus. From about 32 to 36 weeks, the patient had a recurrent sore throat and increased abdominal distension such that twins were suspected. When examined on December 28, 1823, the cervix was dilating and the fetal head already partially descended. On December 29, she had an obstructed labor, and the child died intrapartum, probably due to delay in the second stage. Bennewitz remarked that the baby was of “such robust and healthy character whom you would have thought Hercules had begotten.” The infant weighed 12 lb, a fact witnessed carefully. Postpartum, in spite of continued dieting, sweating and purging, and the application of eight leeches, the patient’s strength improved daily, and sugar disappeared from her urine. “With nature to preserve and treat her, we dismissed our patient cured.”

Unfortunately, there is no record of the woman’s subsequent health, perhaps because Dr. Bennewitz presented his thesis within 6 months and, having been successful in obtaining his doctorate, dropped out of academic medicine. This pregnancy would certainly qualify as “carbohydrate intolerance of varying severity with onset or first recognition during pregnancy”—which was the definition agreed for gestational diabetes at the first workshop-conference in Chicago in 1980.

Matthews Duncan graduated in Aberdeen and became one of the leading obstetricians of his day. This compilation of cases from the literature, from anecdotal reports, and from his own experience first identified the serious problem of diabetes to the obstetrical world. He recorded at least 22 pregnancies in 15 mothers between the ages of 21 and 38 (the data are confused in places): the mother survived the pregnancy for long enough to become pregnant again in 9 instances, in 5 died at the delivery, and in 6 within a few months. The cause of maternal death was usually diabetic coma, although it is not possible to exclude eclampsia, and some must also have developed puerperal sepsis, and one died from exacerbation of tuberculosis. Out of the 22 babies, 12 died, usually in utero, and they

were usually of a large size: at least 10 survived and only 3 miscarriages are recorded; another 20 pregnancies seem to have occurred before the recorded cases, so some of these mothers must represent late-onset type 2 or gestational diabetes, and these seemed to have a better prognosis for both mother and child.

So far as is known, all, with one exception, were multipara, the pregnancy of highest number being the tenth. They cannot be read without giving a strong impression of the great gravity of the complication, but they are not sufficiently numerous to justify any statistical argument based on the number of occurrences.

The histories further show that

- Diabetes may come on during the pregnancy.
- Diabetes may occur only during pregnancy, being absent at other times.
- Diabetes may cease with the termination of the pregnancy, recurring some time afterwards.
- Pregnancy may occur during diabetes.
- Pregnancy and parturition may be apparently unaffected in its healthy progress by diabetes.
- Pregnancy is very liable to be interrupted in its course, and probably always by the death of the foetus.

Whitfield Williams was professor of obstetrics at Johns Hopkins University and wrote the first major American textbook on obstetrics, which still survives today in the eighteenth edition. He was concerned that the demonstration of sugar in the urine in pregnancy would be overinterpreted. “I know of no complication of pregnancy the significance of which is more variously interpreted than the presence of sugar in the urine of pregnant women.” Williams blamed Matthews Duncan²⁹ for concluding that the detection of sugar in the urine constituted one of the most serious complications of pregnancy, as Duncan’s views were accepted without question, although they were based on a small series of 22 pregnancies in 16 women collected from the then medical literature over 60 years, and his own small experience in Aberdeen. Williams³⁰ presented six case reports to illustrate the various conditions in which sugar may be observed in the urine of pregnant women: simple lactosuria, transient glycosuria (two cases), alimentary glycosuria, recurrent glycosuria, and mild diabetes. All resulted in a normal pregnancy outcome (although all the recorded birth weights were >8 lb). He then analyzed the urinary records of 3000 consecutive patients in the obstetrical department of Johns Hopkins Hospital, in 167 of whom sugar had been demonstrated by Fehling’s solution. He concluded that 137 of these represented definite postpartum lactosuria, being recognized only during lactation, and that almost all the others who had been recognized in late pregnancy were similar. He was able to accurately distinguish glucose from lactose in a few cases and found only 2 of the 167 cases had definite glycosuria and could thus be considered to have mild diabetes complicating pregnancy. This may be the first evidence of screening

for gestational diabetes, suggesting a rather low prevalence in hospital practice in Baltimore, MD, nearly 100 years ago.

The major difficulty in the bedside measurement of reducing sugars by Fehling's test is no longer apparent, as all test strips now use a glucose oxidase system and recognize only glucosuria (lactosuria will still occur but no longer causes medical concern). Whitfield Williams then tabulated all reported cases (81) of diabetes complicating pregnancy from 1826 to 1907: he considered 15 cases to be doubtful, as glycosuria disappeared after delivery (including the famous patient first reported by Bennewitz in 1826, although he had not read the full case report in the original Latin). He calculated an overall immediate maternal mortality of 27%, with an additional 23% of mothers dying within the following 2 years. He concluded: "Pregnancy may occur in diabetic women, or diabetes may become manifest during pregnancy; either is a serious complication, although the prognosis is not so alarming as is frequently stated."

Joslin was the first internist to specialize in diabetes and wrote the first textbook on the subject. In 1915, 6 years before the discovery of insulin, he was able to describe seven personal cases of moderate or severe diabetes associated with pregnancy. He wished to take a more hopeful view, but admitted that little progress had been made. Of his seven cases, four were dead—one by suicide, one with uremic manifestations (eclampsia), one of diabetic coma while under the care of a clairvoyant, and the fourth, having survived one pregnancy with a healthy child, died of pulmonary tuberculosis 2 months after losing her second child. But he was pleased that of the three remaining cases, one was in exceptionally good health, free from sugar, and had a normal child, another in a tolerable condition having been pregnant three times but with only one child now living, and the remaining case alive although severely ill with diabetes 6 years after confinement. He closed his paper with an optimistic comment: "It is certainly true that with the improvements in the treatment of diabetic patients [he meant strict diet], diabetic women will be less likely to avoid pregnancy."

The immediate postinsulin period was marked by some euphoria by both patients and their doctors, but it took a long time for the very considerable fear of pregnancy to diminish and to some extent that fear remains to the present day. A careful retrospective assessment of those early years of insulin at the Rigshospitalet in Copenhagen from 1926 to 1938 showed that although there had been no maternal deaths in 22 pregnancies in 19 diabetic women mostly

treated with insulin (probably the more severe and often referred cases), the perinatal mortality was still 57%.³¹ The 13 perinatal deaths included 6 stillbirths, 2 intrapartum deaths, and 5 early neonatal deaths; of the 10 living children, 3 were asphyxiated at birth, 1 weighed only 1500 g, and 1 was 5250 g. Histological examination of the pancreas in two full-weight fetuses showed a pronounced increase in the size and number of the islets of Langerhans. Dr. Brandstrup, who was in charge of these mothers' care during that time, set the scene for the future advances made by his successor Dr. Jorgen Pedersen after the war.

Brandstrup noted that most of his patients had been considered to be well adjusted with insulin treatment, but that they still had high levels of blood sugar for the greater part of the day. He had previously undertaken physiological studies in pregnant rabbits on the passage of carbohydrates across the placenta after intravenous injection and had shown that while glucose and pentoses passed across by a process of slow diffusion, the placental membrane was almost impermeable to disaccharides, including saccharose and lactose.³² He described one case treated in 1927, illustrated by a 24-hour curve for blood sugar, who had been treated with two doses of insulin daily, felt well, and was looked upon as treated adequately, but he was unhappy with the level of control achieved:

The blood sugar is seen to keep at very high levels through a great part of the day. This feature is typical of the severe cases of diabetes under treatment with insulin, and it explains why the children are subject to intrauterine obesity through excessive supply of sugar also now in the epoch of insulin therapy. But these children are not only fat: they are large too. They present a condition of universal macrosomia ... it seems probable that it is the maternal hyperglycaemia alone that brings about the pathologic-anatomical changes in the child.

Conclusion

There is no doubt that had insulin not been discovered in 1922, then the present-day outlook for successful pregnancy in a diabetic mother would still remain very poor because of continued maternal hyperglycemia, in spite of the enormous improvements in social, medical, and obstetrical care that have occurred in the intervening years.

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3 Metabolism in normal pregnancy

Emilio Herrera and Henar Ortega-Senovilla

Introduction

During pregnancy, the mother adapts her metabolism to ensure the continuous supply of nutrients to the fetus in order to sustain its exponential growth. Of the nutrients that cross the placenta, glucose is quantitatively the most important, followed by amino acids. Although lipids cross the placenta in much lower quantities, maternal lipid metabolism is consistently and intensely affected during pregnancy in order to satisfy both maternal and fetal needs. Fetal growth and development also depend on other essential nutrients, like vitamins. The metabolism of certain vitamins is therefore affected during pregnancy to ensure their proper availability to the fetus. The purpose of this chapter is to review the main changes in carbohydrate, amino acid, lipid, and vitamin metabolisms that take place throughout pregnancy under normal conditions.

Carbohydrate metabolism

Glucose is the primary energy source of fetoplacental tissues. During early pregnancy, both glucose tolerance and insulin sensitivity are normal or greater than normal¹ and the insulin responses to oral glucose are also greater than normal,² whereas hepatic basal glucose production is normal.³ However, by the third trimester of pregnancy, a progressive insulin resistance develops,^{4,5} and an increase in basal and postprandial insulin concentrations is seen.⁶ During late pregnancy, the mother develops hypoglycemia, which is especially conspicuous under fasting conditions, when the rate of gluconeogenesis from different substrates is increased.^{7,8} The use of different substrates for the increased gluconeogenesis is variable: the conversion of glycerol rather than other more classical gluconeogenic substrates, like pyruvate or alanine, to glucose is especially intense.⁹ The development of maternal hypoglycemia, despite the increased gluconeogenesis and the reduced consumption of glucose by maternal tissues caused by her insulin-resistant condition, is the result of the high rate of placental transfer of glucose, which is greater than that of any other substrate.^{10,11} The predominance of glucose transfer by the placenta is brought about by

facilitated diffusion according to concentration-dependent kinetics, thanks to the presence of a high number of glucose transporters, particularly GLUT1.^{11,12} The fetus does not synthesize glucose, but uses it as its main oxidative substrate. This causes fetal glycemia normally to be lower than that of its mother, allowing a positive maternal–fetal glucose gradient, which facilitates its placental transfer.

An increased contribution of carbohydrate to oxidative metabolism occurs in late pregnancy, which is commensurate with the increased rate of glucose production. The 24-hour respiratory quotient (RQ) has been shown to be higher in late pregnancy than postpartum.¹³ Since glucose utilization by maternal tissues during late pregnancy is reduced,¹⁴ the higher RQ seems to reflect the obligatory use of glucose by the fetus,² which uses an estimated 17–26 g glucose/day in late pregnancy,¹⁵ such values being well within the increment in carbohydrate oxidation found in pregnancy.

Protein and amino acid metabolism

The accretion of protein is essential for fetal growth and must be sustained by the active transfer of amino acids from maternal circulation. There is no evidence that pregnant women store protein during early pregnancy, when fetal needs are scarce. Therefore, the increased requirements of late pregnancy must be met by metabolic adjustments that increase both dietary protein utilization and nitrogen retention in order to satisfy fetal demands. Protein metabolism changes gradually throughout gestation so that nitrogen conservation for fetal growth achieves its full potential during the last quarter of pregnancy.^{16,17} Nitrogen balance studies showed that the rate of maternal nitrogen retention between 20 and 40 weeks of gestation was greater than the predicted need,¹⁸ leading to the proposal that the mother gains additional protein in her own tissues. The increased nitrogen retention in late pregnancy is due to a reduction in urinary nitrogen excretion as a consequence of decreased urea synthesis,¹⁶ which is a reflection of amino acid oxidation. It is therefore suggested that, during late pregnancy, there is a shift in the partitioning of amino acids toward net tissue deposition and away from oxidation.¹⁹ Thus, in

late pregnancy, nitrogen balance is modified to allow a more efficient use of dietary proteins.²⁰

Although these alterations in protein metabolism during late pregnancy favor nitrogen conservation, pregnancy is associated with hypoaminoacidemia, which is especially evident during fasting, is present at early gestation, and persists throughout pregnancy.^{21,22} Since insulin infusion in nonpregnant adults decreases both plasma amino acid levels and protein breakdown, it is proposed that the decrease in plasma amino acids found during normal pregnancy is not associated with the insulin resistance condition of pregnancy. Thus, maternal hypoaminoacidemia reflects increased placental amino acid uptake. Additionally, maternal oxidation of branched-chain amino acids decreases in late pregnancy, increasing their availability for transfer to the fetus.²³

In contrast to glucose, the concentrations of most amino acids in fetal plasma are higher than those found in the mother, because placental transfer of amino acids is carried out by an active process, using selective transporters and metabolic energy.^{24,25} This capacity to concentrate amino acids on the fetal side of the placenta against the concentration gradient is clearly seen in the fed and 24-hour fasted rat. As shown in Figure 3.1, under fed conditions, maternal total plasma amino acid levels are similar in 20-day pregnant rats and sex- and age-matched virgin animals, whereas the levels in fetal plasma are already higher than in the mother. However, after fasting, the decline of plasma amino acids in the late pregnant rat is greater than that seen in virgin animals, whereas fetal total plasma amino acid concentration remains the same as when fed. Thus, under fasting, the fetal/maternal total amino acid ratio becomes even higher than when fed, showing the efficiency of the placenta in transferring amino acids against the gradient. A multiplicity of factors affects the overall placental amino acid delivery rates, including the activity and location of the amino acid transporter systems, changes in placental surface area,

uteroplacental blood flow, and maternal concentrations of amino acids,²⁴ all of which change as gestation advances and are dependent on maternal health.²⁶

Lipid metabolism

Accumulation of fat depots in maternal tissues and maternal hyperlipidemia are characteristic features during normal pregnancy. Although lipids cross the placenta with difficulty, essential fatty acids (EFA) and long-chain polyunsaturated fatty acids (LCPUFA) are needed for fetal growth and development and must arrive from maternal circulation. Thus, throughout pregnancy, there are major changes in lipid metabolism.

Adipose tissue metabolism

Fat accumulation takes place during the first two-thirds of gestation^{27,28} and represents an important contribution to the increase in maternal body weight that take place during pregnancy.²⁹ It is the result of both hyperphagia and increased lipid synthesis and is driven by the greater responsiveness to insulin by adipose tissue that occurs during early pregnancy.³⁰ During this early stage of pregnancy, there is also an increase in adipose tissue lipoprotein lipase (LPL) activity as reported in women³¹ and in rats,³² which catalyzes the hydrolysis of circulating triacylglycerols (TAGs) that are carried in TAG-rich lipoproteins (i.e., chylomicrons and very-low-density lipoproteins [VLDLs]). The hydrolytic products, nonesterified fatty acids (NEFAs) and glycerol, are taken up by the subjacent tissue,³³ and overall these changes facilitate the accumulation of lipids in maternal depots.

Further increments in maternal fat depots cease during the third trimester of gestation as a consequence of two changes: (1) a decrease in the LPL activity,³⁴ which mainly corresponds to that present in adipose tissue³⁵ and causes a decline in the hydrolysis and uptake of TAG circulating in the TAG-rich lipoproteins, and (2) an increased activity of enzymes that cause the lipolysis of adipose tissue TAG stores, which is especially manifest under fasting conditions.^{36,37}

The placental transfer of the products of adipose tissue lipolysis released into the circulation, NEFA and glycerol, is quantitatively low,³⁸ and therefore their main destination is maternal liver. In liver, NEFAs are converted into acyl-CoA, and glycerol into glycerol-3-phosphate, which are partially reesterified for the synthesis of TAG. These are released back into the circulation in the form of VLDL, as maternal liver production is increased. In addition, glycerol is also used as a preferential substrate for gluconeogenesis, and NEFAs are used for β -oxidation, leading to energy production and ketone body synthesis. These pathways are markedly increased under fasting conditions in late pregnancy.^{8,39} Ketone bodies easily cross the placenta.⁴⁰ Although not synthesized by the fetus, they reach the same concentration in fetal circulation as in the mother's.⁴¹ In contrast to what occurs in adults, ketone bodies can be used by the fetus not only as energetic fuels but also as substrates for brain lipids.^{42,43}

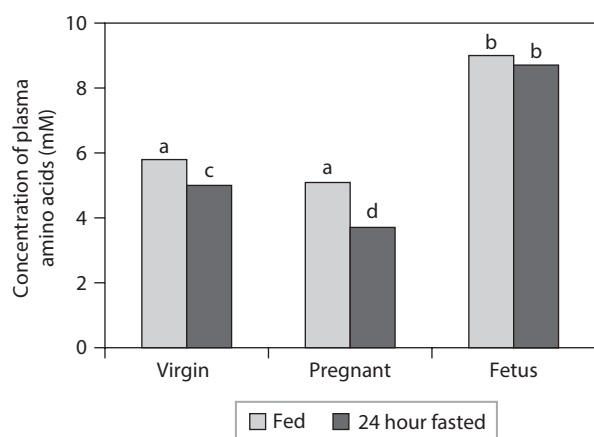


Figure 3.1 Plasma concentration of total amino acids in fed and 24-hour fasted virgin and 20-day pregnant rats and their fetuses. Letters above each bar correspond to the statistical comparison between the groups: different letters indicate statistical differences ($p < 0.05$).

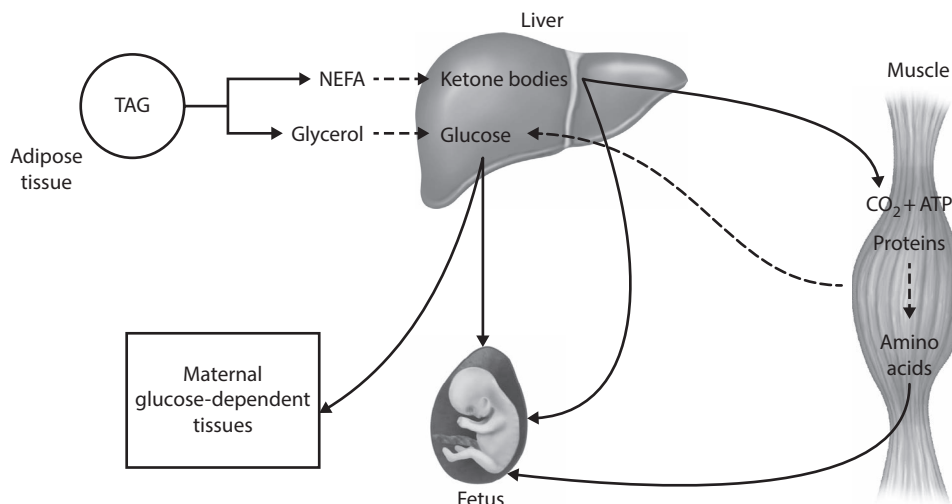


Figure 3.2 Schematic representation of maternal response to starvation during late pregnancy. Enhanced adipose tissue lipolysis increases the availability of glycerol in the liver, where it is used as the preferential substrate for gluconeogenesis, and of non-esterified fatty acids (NEFA) for ketogenesis. This mechanism enables the mother to preserve other gluconeogenic substrates, such as amino acids (mainly, alanine), and ensures their availability to the fetus while producing glucose for the fetus and her own needs. *Note:* TAG, triacylglycerols.

Thus, as shown in Figure 3.2, both the mother and the fetus benefit from the increased adipose tissue lipolytic activity during late pregnancy, especially during periods of fasting. The preferential conversion of glycerol to glucose allows the preservation of other gluconeogenic substrates like alanine and other amino acids for transfer to the fetus. The active production of ketone bodies from fatty acids by fasting maternal liver allows both their transfer to the fetus and their use by maternal tissues such as skeletal muscle as alternative fuels. Ketone bodies also save glucose for its use by maternal tissues, like the nervous system that depends on glucose, and for its transfer by the placenta.

Pregnancy hormones may contribute to some of the changes taking place in adipose tissue metabolism. Figure 3.3 summarizes the main pathways of adipose tissue metabolism, showing how representative hormones exert active control on them. Insulin augments LPL activity and therefore increases the uptake of circulating TAG-rich lipoproteins, whereas it decreases the adipocytes' lipolytic activity. This later effect is achieved by increasing the conversion of cAMP into AMP and consequently decreasing the activator of the protein kinase A, which is responsible for the breakdown of intracellular TAG through the phosphorylation and activation of several key proteins like perilipin, adipocyte TAG lipase, and hormone-sensitive lipase (HSL).

On the other hand, lipolytic hormones increase the activity of the lipolytic cascade by increasing the activity of adenylate cyclase and consequent production of cAMP, as is the case for glucagon and catecholamines, by interacting with their respective receptors (Figure 3.3).

In early pregnancy, increased estrogen, progesterone, and insulin favor lipid deposition and inhibit lipolysis. However, in late pregnancy, placental hormones like human chorionic somatotropin add to the effect of the insulin resistance by promoting lipolysis and fat mobilization. This shift from an anabolic to a catabolic state is further accelerated under

fasting conditions, where maternal hypoglycemia seems to be responsible for an increase in catecholamine production⁴⁴ and consequently for increasing the breakdown of fat depot and promoting the use of NEFA and glycerol by maternal tissues while preserving glucose and amino acids for the fetus.

Hyperlipidemia

Hyperlipidemia normally develops during the last third of gestation and mainly corresponds to increases in TAGs, with smaller rises in phospholipids and cholesterol.^{29,34} As well as the increase in VLDL levels described earlier, the increase in plasma TAGs also results from their proportional enrichment in both low-density lipoprotein (LDL) and high-density lipoprotein (HDL),³⁴ lipoproteins that are normally poor in TAGs. Such changes in the maternal lipoprotein profile and composition are the result of the combined action of several factors, which are schematically summarized in Figure 3.4: (1) the arrival of larger amounts of the adipose tissue lipolytic products, NEFA and glycerol, at the liver, which facilitates the hepatic synthesis of TAGs, and their subsequent release into the circulation as VLDL; (2) a decreased removal of VLDL from the circulation as a consequence of the reduced adipose tissue LPL activity; (3) an increase in cholesteryl ester transfer protein activity that takes place at midgestation,⁴⁵ facilitating the transfer of cholesterol from LDL and HDL to VLDL in exchange for TAGs; and (4) the intense decrease in hepatic lipase (HL),³⁴ which results in less conversion of the relatively buoyant HDL_{2b} TAG-rich particles into smaller TAG-poor and cholesterol-rich particles (HDL₃), allowing the former to accumulate in the circulation.³⁴

Plasma estrogen increases hepatic VLDL production⁴⁶ and decreases HL expression and activity.⁴⁷ Consequently, the increase in its concentration during gestation will add to the effects of the insulin resistance⁴⁸ and contribute to the maternal hypertriacylglycerolemia.

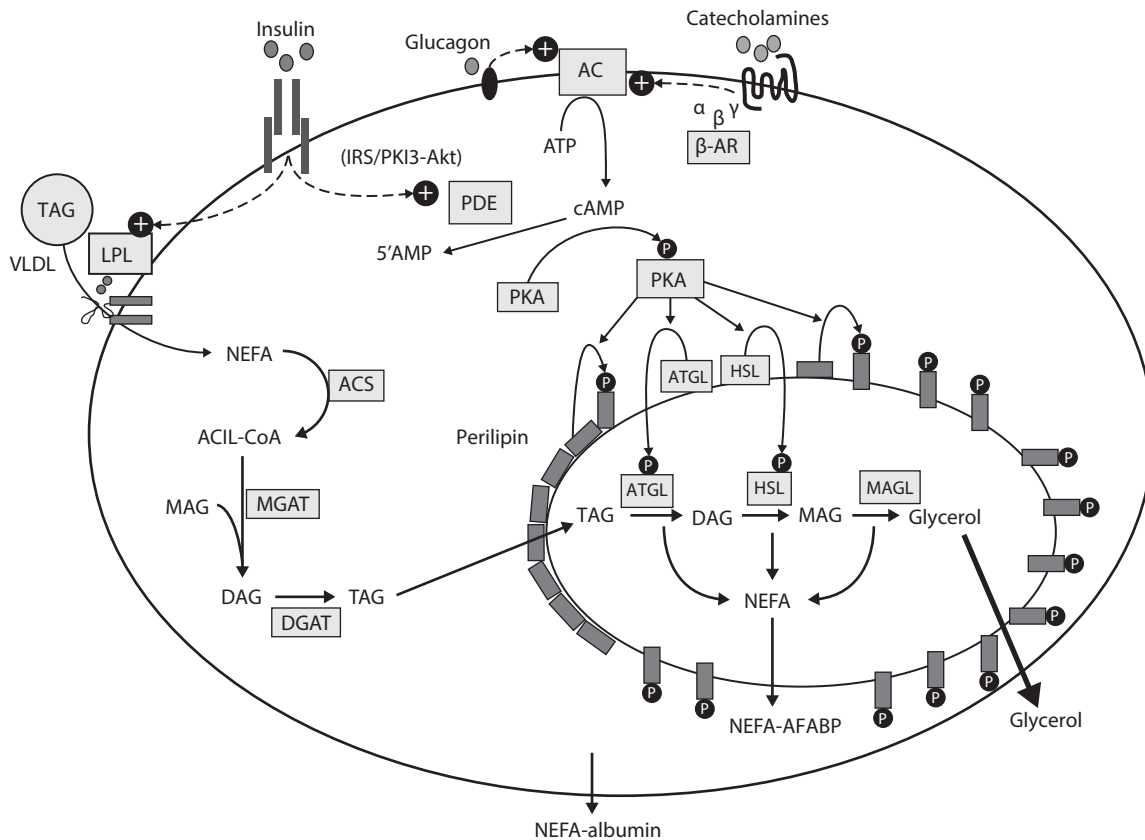


Figure 3.3 Overview of adipose tissue lipolysis and the uptake of circulating triacylglycerol (TAG)-rich lipoproteins (mainly very-low-density lipoprotein [VLDL]) and their control by insulin, glucagon, and catecholamines. The binding of glucagon or catecholamines to their respective receptors (in case of catecholamines to the β -adrenergic receptors, β -AR) activates adenylate cyclase (AC) and increases the production of cyclic AMP (cAMP). This leads to the activation of protein kinase A (PKA), which phosphorylates and activates several key proteins including perilipin, adipocyte triacylglycerol lipase (ATGL), and hormone-sensitive lipase (HSL). Phosphorylation of perilipin modifies its barrier function, resulting in a restructuring of the surface of the lipid droplet, and allows access by the lipases to the lipid droplets. The translocation of ATGL and HSL from the cytosol to the lipid droplet results in the sequential hydrolysis of TAGs to diacylglycerols (DAG) and then to monoacylglycerols (MAG), which are hydrolyzed by monoacylglycerol lipase (MAGL) producing nonesterified fatty acids (NEFAs) and glycerol. Glycerol is directly released into the circulation; the NEFAs are bound to adipocyte fatty acid binding protein, which facilitates their intracellular trafficking from the droplet surface to the plasma membrane as part of their efflux from the cell. In plasma, the NEFAs circulate bound to other binding proteins (fatty acid binding proteins), of which albumin is the most abundant. Insulin also has many effects, most of which oppose the effects of glucagon and catecholamines. It stimulates lipoprotein lipase (LPL) activity, increasing the hydrolysis of circulating TAGs of TAG-rich lipoproteins (mainly VLDL), to facilitate the uptake of released NEFA, which are converted to TAG inside the cell, and has an antilipolytic action by its activation on the phosphodiesterase (PDE) activity, which converts cAMP into 5'-AMP. This mechanism reduces intracellular concentrations of cAMP, resulting in an inhibition of lipolysis. Conditions causing an insulin resistance, as is the case in late pregnancy, prevent these two effects of insulin, i.e., they decrease LPL activity and increase lipolytic activity. These actions are exaggerated at late pregnancy by the actions of catecholamines and lipolytic hormones produced by the placenta. ACS, acyl-CoA synthetase; MGAT, acyl-CoA monoacylglycerol acyltransferase; DGAT, acyl-CoA diacylglycerol acyltransferase.

Benefits of maternal hypertriacylglycerolemia to the fetus and newborn

Although maternal TAGs do not directly cross the placenta,⁴⁹ we think that there are several ways by which the fetus and newborn may benefit from maternal hypertriacylglycerolemia:

1. Use of TAGs as metabolic fuels. Although adult liver does not normally express LPL activity, studies in the rat have shown that under fasting conditions during late pregnancy, there is a marked increase in liver LPL activity.⁵⁰ This liver LPL seems to be the result of the washout of LPL from extrahepatic tissues carried out by the remnants of the TAG-rich lipoproteins. In this way, under
2. Placental transfer of polyunsaturated fatty acids (PUFA). EFA from the maternal diet and LCPUFA, derived either from the diet or by endogenous synthesis from EFA, are mainly transported in their esterified form in maternal plasma lipoproteins rather than as NEFA.⁵¹ The placenta expresses receptors for all the major plasma

fasting conditions, the maternal liver switches from an exporter organ to an importer of plasma TAGs, which may be used as substrates for ketogenesis. This allows the exaggerated increase in plasma ketone bodies, which, as discussed earlier, save glucose in maternal tissues and cross the placental barrier providing a substrate for the fetus.

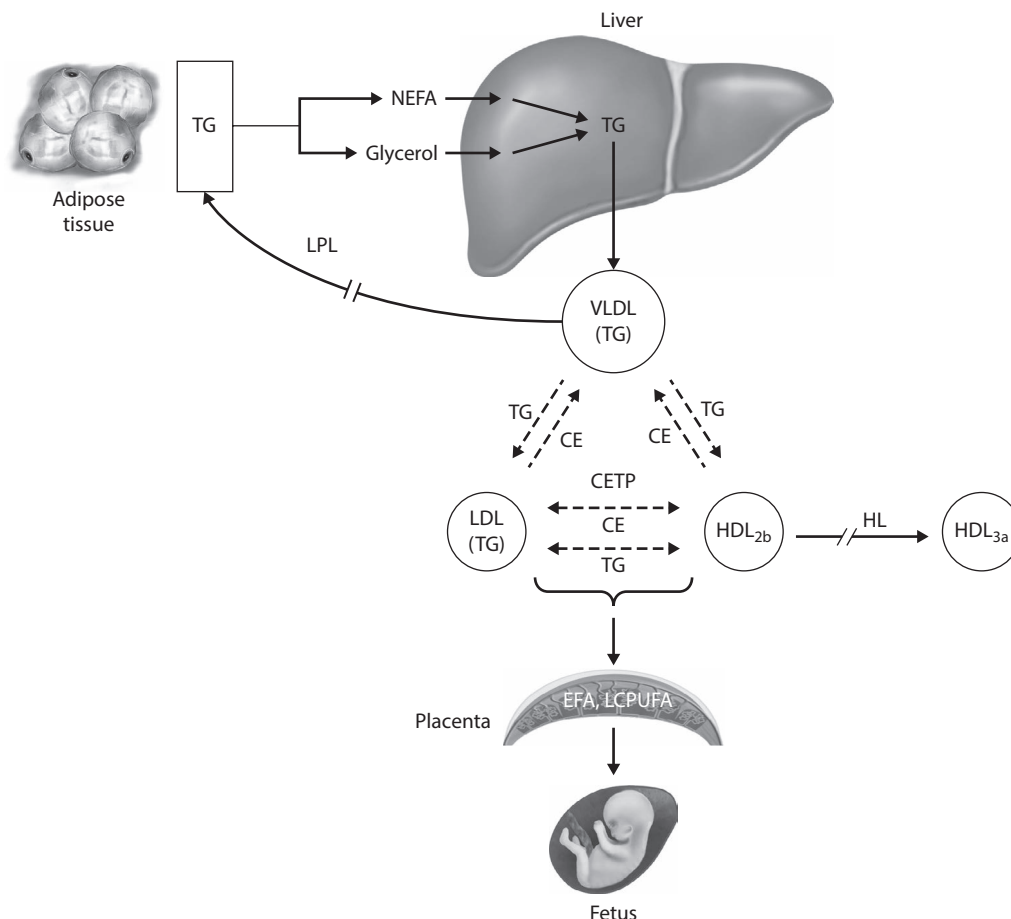


Figure 3.4 Schematic representation of the relationship of adipose tissue lipolytic activity with lipoprotein metabolism during late pregnancy, and its role as a source of essential (EFA) and long-chain polyunsaturated fatty acids (LCPUFA) for the fetus. CE, cholesterol esters; CETP, cholesterol ester transfer protein; HDLs, high-density lipoproteins; LDLs, low-density lipoproteins; VLDLs, very-low-density lipoproteins; LPL, lipoprotein lipase; HL, hepatic lipase; TG, triacylglycerols.

lipoproteins. It has different lipolytic activities, including LPL, phospholipase A₂, and an intracellular lipase, and it also expresses fatty acid binding proteins (for a review, see Herrera et al.⁵²). Thus, esterified PUFA in maternal plasma lipoproteins are taken up either intact through the placenta's receptors or after hydrolysis as their constituent fatty acids. Within the placental tissue, the fatty acids are reesterified to be subsequently hydrolyzed along with those taken up intact and finally diffused into the fetal plasma by a mechanism that is not yet completely understood. This process, together with the direct transfer of NEFA and the intrinsic placental fatty acid metabolism, determines the actual rate of the selective placental fatty acid transfer, which is essential for fetal development.

3. Contribution to milk synthesis in preparation for lactation. Around parturition, there is a rapid rise in mammary gland LPL activity⁵³ that, together with the low LPL activity in adipose tissue,³⁵ drives circulating TAGs to the mammary gland. This caused a rapid disappearance of maternal hypertriacylglycerolemia,³⁴ and EFA and LCPUFA from maternal circulation are taken up by the mammary gland for milk synthesis to become available to the suckled newborn, contributing to its normal development.

Adipocytokines and fetal growth

Adipose tissue secretes several specific proteins called adipocytokines that play critical roles in energy homeostasis in adults, and some of them also modulate insulin action in different tissues.^{54,55} Changes in the plasma levels of some of these adipocytokines during pregnancy are involved in the maternal changes of insulin sensitivity and are known to contribute to fetal growth. Here we will describe four adipocytokines that are known to possess this property: adipocyte fatty acid binding protein (AFABP), leptin, adiponectin, and retinol binding protein 4 (RBP4).

AFABP is responsible for the intracellular trafficking of fatty acids and interacts with HSL increasing its lipolytic activity.⁵⁶ This novel adipocytokine is present in human serum⁵⁵ and its concentrations are associated with insulin resistance and type 2 diabetes,⁵⁷ being higher in pregnant women with gestational diabetes mellitus (GDM) than in control subjects.⁵⁸ The concentration of AFABP in cord serum of control subjects is higher than in the corresponding maternal serum, and in GDM fetuses, values correlate with neonatal fat mass.⁵⁸

Leptin is produced by adipose tissue as well as by other tissues, including the placenta,^{59,60} its concentration in maternal plasma being increased during late pregnancy.⁶⁰

Besides increasing adipose tissue lipolysis, leptin modulates glucose metabolism and insulin sensitivity, and maternal hyperleptinemia seems to contribute to the availability of nutrients to the fetus. Although the relationship between fetal leptin and birth weight has not been clearly established, leptin concentration in serum from the umbilical vein has a strong positive correlation with neonatal fat mass⁶¹ and is considered a marker of adiposity in the fetus.

RBP4 is another adipocytokine that has been shown to regulate glucose metabolism by reducing insulin sensitivity.⁶² During pregnancy, RBP4 is also synthesized by the placenta, and its concentration in maternal plasma increases progressively with gestational age as the placenta expands.⁶³ The concentration of RBP4 in maternal and cord blood serum is higher in pregnant women with GDM than in controls,⁵⁸ and it has been proposed that this contributes to the higher insulin resistance found in women with GDM.

Adiponectin is another adipocytokine, but unlike the foregoing examples, it increases insulin sensitivity. During normal pregnancy, no significant alterations in adiponectin levels have been found,⁶⁴ but its levels negatively correlate with insulin resistance⁶⁵ and they are lower in women with GDM than in control women.⁶⁶ Cord blood adiponectin concentrations increase with gestational age and correlate positively with birth weights,⁶⁷ suggesting a possible role in fetal adiposity and development. However, cord blood adiponectin concentrations in women with GDM are lower than in controls, and no relationship is found between this variable and neonatal fat mass or birth weight.⁵⁸

Vitamin metabolism in pregnancy

Adequate maternal micronutrient and vitamin status is especially critical during pregnancy and lactation. Several micronutrient deficiencies (like iron, iodine, zinc) are well established as contributors to abnormal prenatal development or pregnancy outcome. Less well recognized for their importance are deficiencies of vitamins. Evidence is accumulating that maternal antioxidant status is important to prevent abnormal pregnancy outcomes. In lactation, the maternal status of several of these vitamins affects their concentration in breast milk. The main cause of multiple vitamin deficiencies is a poor-quality diet, even though gene polymorphism can also impair vitamin absorption or alter their metabolism and cause vitamin deficiency.

We summarize here the changes in the metabolism of the vitamins during pregnancy that have the highest implications in fetal growth and development.

Hydrophilic vitamins

Folic acid

Folates act in a number of one-carbon transfer reactions, including purine and thymidylate biosynthesis, amino acid metabolism, and formate oxidation. Purine and thymidylate biosyntheses are fundamental requirements underlying

DNA and RNA synthesis. Thus, it is obvious that these folate-dependent reactions are essential for fetal growth and development and for maternal well-being.

Pregnancy is associated with an increased folate demand and, in some cases, leads to overt folate deficiency. The increase in folate requirement during pregnancy is due to the growth of the fetus and uteroplacental organs. Circulating folate concentrations decline in pregnant women who are not supplemented with folic acid.⁶⁸ Possible causes for the declines in blood folate include an increased folate demand for the fetus, increased folate catabolism, increased folate clearance and excretion, decreased folate absorption, hormonal influence on folate metabolism as a physiological response to pregnancy, and low folate intake.^{69,70} There is a strong positive association between folate concentrations in maternal plasma, cord plasma, and placenta, suggesting that transplacental folate delivery depends upon maternal plasma folate concentrations. The transfer of 5-methyltetrahydrofolate (the main form of folate in plasma) from the maternal to the fetal perfusate is not saturable in a range well above typical physiological concentrations⁷¹; also it is favored by the folate receptor, which is abundant in the epithelial cells of placenta.⁷²

Studies conducted in recent years led to the recognition that supplementing the maternal diet with folic acid reduced the prevalence of folate deficiency in pregnancy and prevented pregnancy-related disorders. Data from these studies suggest that 200–300 µg folic acid per day is needed in addition to dietary folate to maintain normal folate status and to prevent folate deficiency during pregnancy.^{73,74}

Vitamin C

In addition to the prevention of scurvy, vitamin C (or ascorbic acid) has numerous other functions and is a cofactor for several enzyme systems. For humans, ascorbic acid is an essential vitamin, with an important antioxidant function. As antioxidant defense systems are important to protect tissues and cells from damage caused by oxidative stress, an imbalance between increased oxidative stress and decreased antioxidant defenses impairs fetal growth.⁷⁵ Thus, pregnant women utilize a defense mechanism, composed of antioxidant enzymes and nutrients including vitamin C, against oxidative stress and free radical damage. It is believed that ascorbic acid, after conversion to dehydroascorbic acid, crosses the placenta to enter fetal circulation. Once in the fetal circulation, dehydroascorbic acid is reduced back to ascorbic acid and is maintained in high concentrations on the fetal side in the placenta.⁷⁶ Maternal serum vitamin C levels during the second trimester of gestation are correlated with birth weight and length in full-term babies.⁷⁷

Lipophilic vitamins

Because lipophilic vitamins are fat soluble, they share several common mechanisms with other lipophilic substances in terms of their metabolism and transfer to the offspring. Although lipophilic vitamins are essential during

intrauterine and early postnatal life, little is known about their placental transfer during pregnancy or their uptake by mammary gland during lactation.

Vitamin D

Vitamin D metabolites have numerous potential physiological and pharmacological actions, but their principal physiological function is maintaining serum calcium and phosphorus concentrations in a range that supports cellular processes, neuromuscular function, and bone mineralization.

Significant changes in maternal vitamin D and calcium metabolism occur during pregnancy to provide the calcium needed for fetal bone mineral accretion. Fetal concentrations of 1,25-dihydroxy-vitamin D ($1,25(\text{OH})_2\text{D}_3$, the active metabolite of vitamin D_3) are low, whereas maternal levels are strikingly elevated during pregnancy.⁷⁸ This increase in maternal $1,25(\text{OH})_2\text{D}_3$ levels appears to be caused by increased production rather than decreased clearance, but the precise source of the increased $1,25(\text{OH})_2\text{D}_3$ synthesis has yet to be fully defined. $1,25(\text{OH})_2\text{D}_3$ can pass through the placental barrier in either direction to sustain the active transport of calcium across the placenta during late gestation. Approximately, 25–30 g of calcium is transferred to the fetal skeleton by the end of pregnancy, most during the last trimester. It has been estimated that the fetus accumulates up to 250 mg/dL calcium during the third trimester. The three possible calcium sources that could supply the mother with the necessary calcium to support fetal growth include increased intestinal absorption from the diet, increased renal conservation, and increased bone mobilization.⁷⁹

To date, there is no evidence to indicate a beneficial effect of vitamin D intake during pregnancy above amounts routinely required to prevent vitamin D deficiency among nonpregnant women.

Vitamin A

Vitamin A exists in several forms in animal tissues: retinol, retinal, retinoic acid, and retinyl esters, mainly as retinyl palmitate. All forms of vitamin A are hydrophobic compounds, which are highly unstable in the presence of O_2 . A diet deficient in either retinol or the provitamin A carotenoids that can be metabolized to retinol results in impaired growth, night blindness, and, ultimately, xerophthalmia and blindness. We now know that there are two metabolites of vitamin A, retinoic acid and retinal, that are responsible for growth and development by regulating gene expression, whereas retinal and its isomers are responsible for the visual function of vitamin A.

During pregnancy, concentrations of retinol in maternal plasma fall as gestation advances⁸⁰ (Figure 3.5), which probably reflects the increasing demands of the rapidly growing maternal and fetal tissues. It has been shown that retinol plays an essential role in the development of organs such as the lungs, heart, and skeleton, while retinoic acid enables the setting up of the vascular and nervous system and is involved as a morphogenic agent during embryonic development.^{81,82} Multiple fetal anomalies occur in vitamin A deficiency, as well as in knockout mice deficient in the receptor for retinoic acid. An excess of vitamin A also induces the same type of abnormality: the importance of the abnormality depends on the period of gestation and the duration of the excessive or deficient supply.⁸³

The mechanism of transfer of vitamin A from mother to fetus remains unknown, but it allows vitamin A levels in the fetus to remain unaffected by alterations in maternal vitamin A status, except in conditions of deficiency or excess.⁸⁴ The placenta's vitamin A content increases in the last trimester of pregnancy, thanks to the supply of vitamin A from maternal stores (i.e., liver).⁸⁵ Studies in rats showed that in early gestation, maternal RBP (retinol binding protein) is transported across

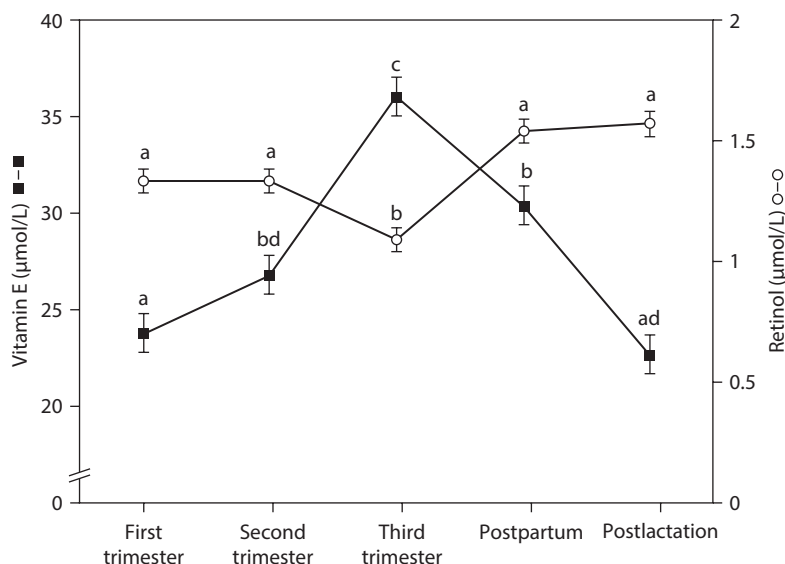


Figure 3.5 Plasma levels of vitamin E (α - and γ -tocopherol) and vitamin A (retinol) in the different trimesters of pregnancy, 6–8 days postpartum and postlactation, in healthy women. Data are expressed as means $\pm$ SEM. Statistical comparisons between the different times are shown by the letters above the points. Different letters for the corresponding vitamin between the groups indicate statistical significance ($p < 0.05$).

the placenta and delivers retinol, whereas in late gestation, a different mechanism appears to be operating because fetal liver is capable of synthesizing RBP.⁸⁶ Studies *in vivo* show that maternal RBP does not cross the placental membrane barrier in the last trimester of gestation and cannot enter fetal circulation,⁸⁷ and homozygous RBP-null mutant mice are viable and fertile.⁸⁸ In humans, serum apo-RBP (retinol-free) concentration appears to be elevated during pregnancy, suggesting that pregnancy may alter the affinity of RBP for retinol or induce the binding of the vitamin to other uncharacterized proteins.⁸⁹ Moreover, other forms of vitamin A, such as retinyl esters and retinoic acid, can also be taken up at the placental barrier.

Nevertheless, there are no significant correlations between maternal and cord plasma concentrations of retinol or carotenoids under normal conditions, although some authors report a weak but statistically significant correlation when the concentrations of retinol in cord and maternal plasma are low.⁹⁰ Published studies in humans show that maternal subclinical vitamin A deficiency is related to neonatal subclinical vitamin A deficiency and to low birth weight^{90,91}; furthermore, adequate vitamin A at delivery is positively associated with birth outcomes and children's neurodevelopment in later childhood.⁹²

The situation with vitamin A in early lactation is peculiar. Because of the limited transplacental transfer, the infant's liver stores of vitamin A at birth are small even in well-nourished populations, so newborns are highly dependent on dietary intake of the vitamin to establish proper tissue stores, maintain rapid growth, and develop their immune system. Colostrum contains a higher vitamin A concentration than milk and has an important role to play in providing the initial protection from vitamin A deficiency in the newborn.⁹³ The timing of colostrum ingestion seems to play a role in the efficiency of intestinal vitamin absorption, thus colostrum feeding on the day of birth is important for the establishment of absorptive mechanism allowing intestinal transport of fat-soluble vitamins. Moreover, breast milk is also a good source of vitamin A and clinical vitamin A deficiency is rare in breast-fed infants during their first year of life.

Debate surrounds the use of retinol supplements during pregnancy. The use of retinol supplements in well-nourished mothers does not affect fetus concentrations. High doses of retinol are teratogenic, and in some countries, pregnant women are advised to avoid retinol-containing supplements.⁹⁴ However, this advice may lead to vitamin A deficiency.⁹⁵ Serum retinol is a relatively insensitive indicator of body vitamin A status: only 1% of the body's reserves circulate in the plasma, and homeostatic mechanisms control concentrations via retinol binding protein concentrations.

Vitamin E

Dietary vitamin E is present as tocopherol, mainly α - and γ -tocopherol, and tocopheryl esters. Plasma levels of vitamin E in the mother increase significantly from the first trimester of gestation to reach a maximum in the third trimester of gestation (Figure 3.5).^{80,96,97} Unlike vitamin A, there is no specific carrier protein in the serum to transport vitamin E,

which circulates as its nonesterified alcohol form in serum lipoproteins. Changes in plasma α -tocopherol levels during pregnancy parallel maternal hyperlipidemia (see earlier in this chapter). In contrast, γ -tocopherol reaches a maximum concentration in maternal plasma at midgestation. The reason for the different concentration patterns (between α - and γ -tocopherol) during pregnancy is unknown, but could be related to differences in their tissue uptake and intracellular metabolism.

α -Tocopherol concentration in the plasma of human fetuses is lower than in their mothers, but rises toward the end of pregnancy. Since α -tocopherol is carried in plasma mainly by VLDL and LDL, its uptake and handling by the placenta are similar to that of the other lipoprotein lipophilic components (see earlier in this chapter). The placenta also expresses α -tocopherol transfer protein (α -TTP), and in a manner similar to its role in liver, it may actively contribute to the specific transfer of α -tocopherol to the fetus.^{98,99}

Despite the existence of all these processes, efforts to investigate the kinetics of the transfer of vitamin E by isolated human placental systems have found that it is specific for the natural stereoisomer, *RRR*- α -tocopherol, rather than any other form of vitamin E, but that its rate is very low. This justifies the consistent finding of much lower α -tocopherol levels in fetal plasma and red blood cells than in maternal ones.

During lactation, vitamin E intake through milk is the way of supplying the newborn with an essential defense against oxygen toxicity and of stimulating the development of its immune system. A good supply of vitamin E to the offspring is therefore particularly critical in this period. The increase in vitamin E content in body tissues of the offspring following birth is attributed to the ingestion of colostrum and milk, emphasizing the limited placental vitamin E transfer and the importance of milk consumption. Colostrum contains a higher concentration of vitamin E than does milk,¹⁰⁰ which may imply an active uptake by the mammary gland in compensation for the limited placental transport. A decline in maternal circulating vitamin E concentration is noticed at the end of gestation or in early lactation; this decrease coincides with the high concentration of α -tocopherol present in colostrum, and the two events are probably related. The mechanism of transfer from blood into milk is not completely understood. Perhaps the transfer of vitamin E into milk occurs through a protein-mediated transport: the presence of an α -TTP-like mechanism in the mammary gland cannot be excluded nor can the presence of a lipoprotein scavenger receptor class B1 (SR-BI receptor) in the mammary gland, which could be involved in the uptake of α -tocopherol from HDL. In addition, the high concentration of vitamin E found in colostrum compared to mature milk might be due to an increase in the activity of mammary LDL receptors and, thus, to an important uptake of LDL by the mammary gland around parturition. LPL also seems to modulate the mammary gland uptake of α -tocopherol from VLDL and chylomicrons.¹⁰¹ In contrast to placental transfer of tocopherols, which remains low even when maternal serum levels are high, the transfer through colostrum and milk can be increased by increasing the ingestion of vitamin E by the mother.

It is important to note that tocopherol is able to affect the metabolism of vitamin A in several tissues and may play a role in tissue retinol homeostasis. It has been shown to modulate the levels of retinol and total vitamin A in tissues such as the liver, kidney, and intestine. In vitro, tocopherol exerts an inhibiting or stimulating action (depending on the tissue) on the hydrolysis of retinyl palmitate.

Summary

Maternal metabolic adaptations during pregnancy are mainly directed toward maintaining a continuous availability of substrates to enable fetal growth. Glucose, used as a primary energy source of fetoplacental tissues, is quantitatively the most important substrate crossing the placenta. During late pregnancy, the mother develops hypoglycemia as a result of the high rate of placental transfer, despite there being more active gluconeogenesis and a reduced consumption of glucose.

Amino acids cross the placenta against the concentration gradient, thanks to an active process. Fetal growth is sustained by the transfer of amino acids from the maternal circulation. Protein metabolism changes gradually throughout gestation, and although during late pregnancy there is increased nitrogen retention, the mother develops hypoaminoacidemia, which is especially evident during fasting.

Fat depot accumulation and maternal hyperlipidemia are characteristic features of pregnancy. During late pregnancy, maternal adipose tissue lipolytic activity is increased, and

the main destination of released NEFA and glycerol is the liver, where they are used for the synthesis of TAGs. The glycerol is also used as a gluconeogenic substrate and the NEFAs are also oxidized for ketogenesis.

Adipocytokines secreted by adipose tissue play critical roles in energy homeostasis in adults, and some of them modulate insulin action. Circulating levels of some of these adipocytokines are modified during pregnancy, are involved in the maternal changes of insulin sensitivity, and are appeared to contribute to fetal growth. This is the case for AFABP, leptin, adiponectin, and RBP4.

Major changes also occur in vitamin metabolism. Vitamins A and E are the most affected. Maternal plasma retinol falls as gestation progresses, whereas vitamin E levels increase parallel to the increase in plasma lipids. Transplacental transfer of these vitamins is limited, but both the fetus and the newborn need them. They are both taken up by the mammary gland, and their high concentration in colostrum seems to play an important role in the extrauterine adaptations of the suckled newborn.

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4 Intermediary metabolism in pregnancies complicated by gestational diabetes

Bartolomé Bonet, María Bonet-Alavés, and Isabel Sánchez-Vera

Changes in intermediary metabolism during pregnancy

As has been shown in the previous chapters, major changes take place in the intermediary metabolism throughout pregnancy: changes that will facilitate the fetal needs of energy and precursors for fetal and placental growth, as well as for placental hormone synthesis. From a metabolic point of view, during gestation there are two different periods. In the first half of pregnancy, during the embryo development period, there are maternal changes that lead to storage of energy and nutrients.¹⁻³ During this time of pregnancy, there is both increased appetite and normal or increased insulin sensitivity. These changes will facilitate glucose and lipid uptake by adipose tissue, increasing the lipid stores.¹⁻³ In fact, during the first half of pregnancy, most women show an increase in adipose tissue mass.⁴ Nevertheless, as pregnancy advances and the fetal-placental unit is rapidly growing, a marked shift in the metabolic pathways is observed. This second period is characterized by a state of maternal insulin resistance, decreasing the uptake of glucose in the insulin-sensitive tissues, mainly the white adipose tissue and muscle (Figure 4.1, panel b). Such a condition facilitates the supply of glucose toward the fetus, where the daily glucose requirements are very high (30–50 g of glucose/day).⁵ The insulin resistance is also responsible of the blunted curve that takes place after an oral glucose tolerance test or a regular meal.⁶⁻⁸ Such a curve causes higher and more prolonged plasma levels of glucose after a meal facilitating a higher glucose supply toward the fetus, as the transfer of glucose through the placenta is via passive glucose diffusion and, therefore, concentration dependent.⁹

Plasma lipid changes during pregnancy

During gestation, there are also relevant changes in lipid metabolism (Figure 4.1, panel b), changes most marked in the second half of pregnancy, when both plasma

triglycerides and cholesterol reach the highest levels.^{1,2,10,11} The high plasma levels of triglycerides seem to be secondary to both an increased hepatic synthesis of very-low-density lipoproteins-triglycerides (VLDL-TG) and a decreased lipoprotein lipase (LPL) activity in the adipose tissue in late gestation.^{10,11} These changes are due to some of the hormonal changes observed during pregnancy. The increased production of VLDL-TG is secondary to the elevation of estradiol that takes place during gestation, as increased levels of estradiol stimulate the hepatic synthesis of triglycerides.^{12,13} Both the human placental lactogen, which reaches its maximum concentration by the end of pregnancy, and insulin resistance increase adipose tissue lipolysis, leading to an abundant supply of fatty acids to the liver.^{14,15} The lower levels of adiponectin observed as pregnancy advances^{16,17} may also play a role in the increased hepatic synthesis of triglycerides, as under this condition, in the liver, there is a decrease in beta-oxidation¹⁸ and, therefore, the fatty acids are derived toward reesterification and synthesis of triglycerides. The high plasma levels of triglycerides are used as a source of energy for the maternal tissues, sparing glucose for the fetus and the maternal tissues where glucose is the only source of energy. In addition, they are used by the placenta, where LPL is present¹⁹; therefore, the placenta is able to hydrolyze the VLDL-TG, releasing fatty acids, which are taken up by placental cells.¹⁹ In fact, several studies have shown a positive relationship between maternal plasma triglycerides and birth weight.^{20,21}

The elevation of the plasma levels of cholesterol, mainly from low-density lipoproteins (LDLs),^{1,2,10,11} will facilitate the substrate for the elevated synthesis of steroid hormones that takes place during pregnancy. By the end of pregnancy, plasma levels of estradiol are almost a thousand times higher than in nonpregnant women and progesterone 10 times higher.²² Cholesterol is also a source of precursors for the high synthesis of cell membranes that takes place in the fast-growing fetus.

As occurs in carbohydrates and lipid metabolism, there are changes in protein metabolism throughout pregnancy.

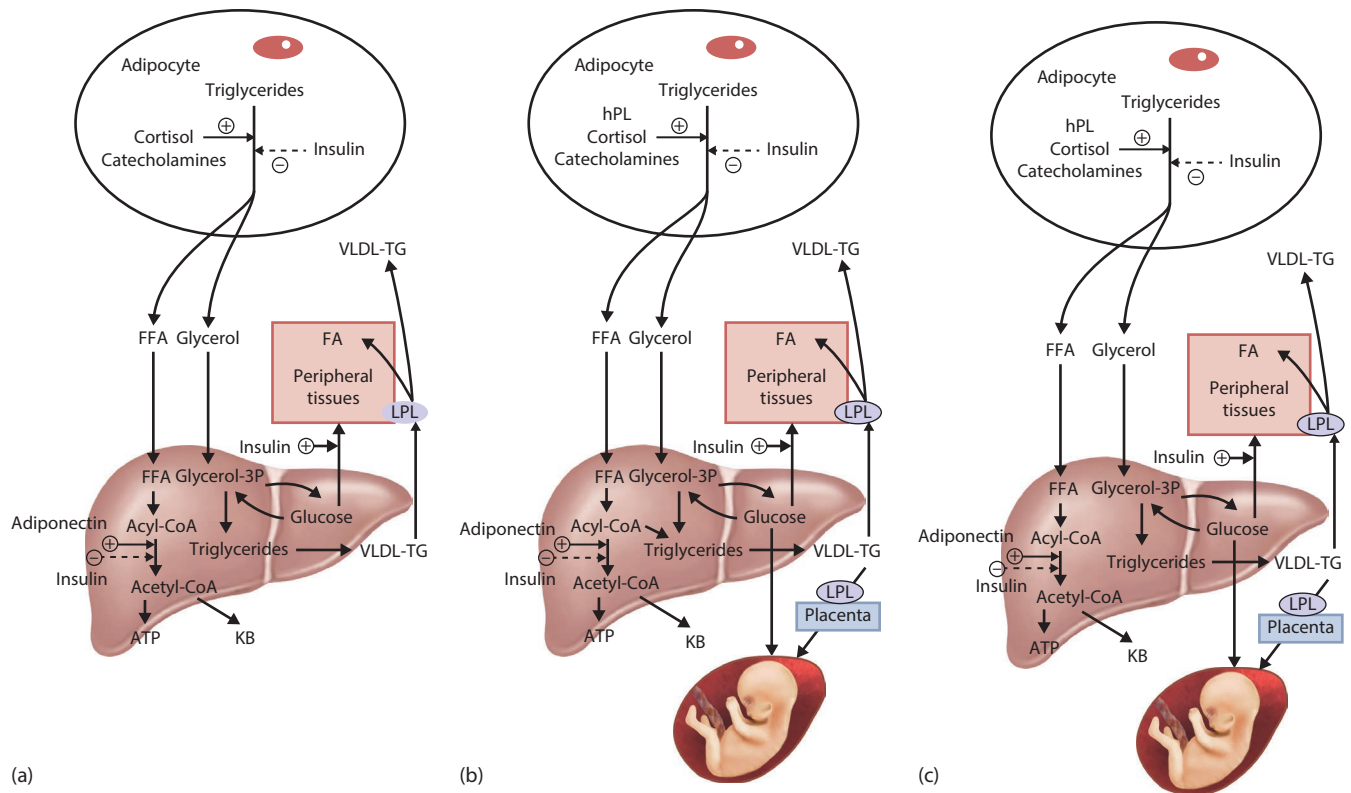


Figure 4.1 Intermediary metabolism in nonpregnant women (panel a), normal pregnancies (panel b), and pregnancies with GDM (panel c). The thickness of the lines relates to the degree of stimulation (solid lines) or inhibition (dash lines) for both the metabolic pathways and the hormonal effects.

These changes develop gradually during gestation. By the end of pregnancy, when fetal growth is maximal, nitrogen retention is four times higher than in early pregnancy,²³ suggesting that amino acids are conserved for tissue synthesis. Nevertheless, the sum of total plasma amino acids declines by 15%–25%, reflecting the enhanced uptake of amino acids by the placenta,²⁴ where there is an energy-dependent active transport,^{24,25} providing a higher concentration of amino acids in fetal plasma. Such a mechanism facilitates the supply of amino acids for the rapid protein accretion that takes place in the fetus by the end of pregnancy.

Overall the metabolic changes observed during pregnancy are directed to supply nutrients to the placental–fetal unit, allowing in a short period of time the fast growing of both elements.

Mechanisms of pregnancy-induced insulin resistance

The mechanisms involved in pregnancy-induced insulin resistance, although not completely understood, seem to be related to the placenta and the increased adipose tissue mass that develops during pregnancy (Figure 4.2). In pregnant rats, there is increased degradation of insulin by the placenta²⁶; therefore, insulin removal is accelerated, causing a higher activity in the pancreatic beta cells. A similar phenomenon may occur in human pregnancies. Both the

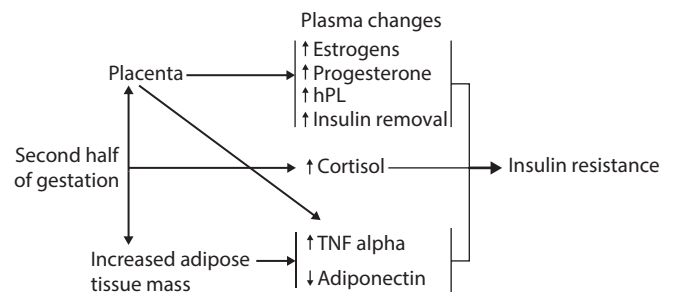


Figure 4.2 Different factors from the placenta and the adipose tissue involved in pregnancy-induced insulin resistance.

placenta and the increased adipose tissue promote important changes in the maternal milieu: hormonal, inflammatory, and metabolic. As pregnancy advances, there is an increase in the plasma levels of placental lactogen and estrogens. The first condition leads to increased lipolysis and to higher plasma levels of free fatty acids¹⁵ that promote peripheral insulin resistance.²⁷ The elevation of estradiol and the decrease in adiponectin promote an increase in the hepatic synthesis and release of triglycerides, such as VLDL-TG; such a condition causes peripheral insulin resistance by increasing the cell metabolism of fatty acids, raising the cellular levels of NADH and ATP. This intracellular condition lowers the glucokinase activity and the cell ability to phosphorylate glucose, decreasing the cell uptake of this substance. The placenta and the higher adipose mass increase the plasma

levels of TNF- α , a condition that modifies the intracellular signaling of insulin, causing insulin resistance.^{28,29} The insulin-sensitizing effects of adiponectin³⁰ are plumbed by the decreased plasma levels of adiponectin observed in the second half of pregnancy. The higher concentration of cortisol found in pregnancy increases the hepatic glucose production and decreases the peripheral tissue glucose utilization, further increasing insulin resistance. The high plasma levels of progesterone found during the second half of pregnancy also has been related with the pregnancy-induced insulin resistance.³¹

Mechanisms leading to the development of gestational diabetes

The mechanisms leading to the development of gestational diabetes mellitus (GDM) have not been fully defined but are probably related to both an exacerbation of the beta-cell dysfunction in subjects genetically predisposed to beta-cell alterations and to the insulin resistance that takes place as gestation advances. In that sense, GDM will act like a type 2 diabetes mellitus (DM). Regarding the beta-cell dysfunction, several mechanisms could be involved in this process. High progesterone levels may play a relevant role.^{32,33} Recently, in models of knockout mice,³³ it has been shown that the lack of progesterone receptors is associated with a higher insulin secretion by beta cells. Therefore, the high levels of progesterone that develop during pregnancy may damage these cells. The hyperlipidemia observed during pregnancy may also decrease the capability of beta cells to secrete insulin.^{34,35} Although fatty acids may induce insulin secretion,³⁶ under certain circumstances, prolonged elevated levels of fatty acids may damage the beta cell, decreasing insulin secretion. In fact, in an experimental animal model during pregnancy, a decrease in plasma free fatty acids (FFA) and triglycerides increases insulin secretion after an oral glucose tolerance test.³⁷ Recently, higher plasma levels of cholesterol have been linked to islet dysfunction³⁸; therefore, pregnancy-induced hypercholesterolemia may play a role in the beta-cell failure associated with GDM.

The higher food intake that develops during early pregnancy may cause beta-cell hyperplasia. In certain genetically predisposed subjects, this higher supply of glucose and fatty acids to the beta cell may increase the cell metabolism, leading to increased beta-cell apoptosis and cell death.^{34,39} Such a phenomenon would compromise the capability of the beta cells to provide enough insulin in a period of increased insulin requirements causing development of GDM. Further research is needed for a better understanding of the beta-cell dysfunction observed in GDM, in order to develop methods to improve this function and decrease the incidence of GDM.

Because the insulin resistance that takes place in the second half of pregnancy plays a key role in the development of GDM, any condition susceptible to exacerbating this resistance may play a role in the development of GDM. Obesity and the associated metabolic alterations also promote

insulin resistance,^{40,41} exacerbating the pregnancy-induced insulin resistance and the risk of developing GDM.

Glucose alterations in GDM

Independent of the mechanisms involved, in GDM, there is a relative lack of insulin during a period of time with high insulin needs to compensate the insulin resistance that develops in the third trimester of pregnancy. When GDM develops, in the maternal tissues, the insulin-dependent glucose uptake is further decreased and hyperglycemia develops. Because the placental transfer of glucose is concentration dependent⁹ under conditions of maternal hyperglycemia and placental normal function, there is increased placental transfer of glucose (Figure 4.1, panel c), and fetal hyperglycemia and, secondary to this alteration, hyperinsulinism develop. As insulin is one of the main growth factors during fetal life,⁴² hyperinsulinemia promotes fetal growth, macrosomia, and complications secondary to the delivery of a large baby, mainly both maternal perineal damage and birth trauma, including shoulder dystocia and Erb's palsy. Once the umbilical supply of glucose is suddenly arrested after delivery, in the newborn, the remaining hyperinsulinism increases the risk of hypoglycemia. The macrosomic newborn will need monitoring of blood glucose within the first hour after birth and early feeds and occasionally may require intravenous administration of glucose.⁴³ Hypoglycemia in the newborn, if not corrected, may lead to brain damage.⁴⁴ Fetal macrosomia also increases the risk of obesity, type 2 DM, and cardiovascular diseases later on in life.^{45,46}

Lipid alterations in GDM

In GDM, as occurs in other conditions of insulin resistance and beta-cell dysfunction, there is an increase in plasma levels of triglycerides and cholesterol. This effect should be added to the physiological hyperlipidemia induced by pregnancy^{10,11} (Figure 4.1, panel c). Therefore, women with GDM have higher plasma levels of triglycerides and cholesterol than found in normal pregnancies.^{47–49} Hypertriglyceridemia found in GDM may also play a role in the fetal macrosomia observed in these pregnancies, as several authors have shown a positive correlation between the plasma levels of triglycerides and birth weight.^{20,21}

Nevertheless, these increased plasma levels of both triglycerides and cholesterol, as occur in other conditions through the life, may have deleterious effects on the normal development of pregnancy and on fetal growth. Increased levels of triglycerides have been associated to structural alterations in LDL.^{50,51} High triglycerides make LDL particles smaller and denser. Such particles are more susceptible to oxidation. Through pregnancy, the maternal milieu changes, developing conditions that both increase and decrease LDL susceptibility to oxidation. Higher levels of triglycerides, cholesterol, glucose, and progesterone

are prooxidant,^{52,53} but this effect may be blunted by higher levels of vitamin E and estradiol,²² two powerful antioxidants whose levels are increased in pregnancy.²² In fact, our group and others have shown that in normal pregnancies, as pregnancy advances, despite increased plasma levels of triglycerides and cholesterol, LDL susceptibility to oxidation decreases,^{22,54} a phenomenon that is partially explained by the high levels of estradiol observed at the end of pregnancy. Nevertheless, under conditions of exacerbated dyslipidemia, the prooxidant effects may lead to increased LDL oxidation and to the consequences associated with this process. An increased LDL oxidation may have relevant consequences for the placenta as well as for the fetus. In a cell culture model of human placental trophoblasts and macrophages, LDL oxidation is cytotoxic.⁵⁵ If this process occurred during pregnancy, it could damage the placenta. If such damage were extensive, the placental capability to transfer nutrients and oxygen to the fetus might be decreased, compromising fetal growth. In fact, our group has shown a correlation between LDL susceptibility to oxidation and birth weight,²² suggesting that in conditions where LDL oxidation is increased, the fetal growth is compromised. Furthermore, when oxidized LDL is taken up by human trophoblasts, through scavenger receptors and not by the LDL receptor, despite increasing the intracellular concentration of cholesterol, progesterone secretion is decreased⁵⁶ (Figure 4.3). These data suggest that the metabolism of cholesterol from oxidized LDL does not follow the physiological pathways required for hormonal synthesis. Therefore, under circumstances of increased LDL oxidation, there may be a lack of cholesterol for the placenta, decreasing the placental synthesis of steroidal hormones as well as the transfer of cholesterol to the fetus. As occurs in other conditions, increased LDL oxidation may also lead to vascular dysfunction,^{57–59} decreasing the vascular blood flow and the nutrient transfer to the fetus. Therefore, increased LDL oxidation could affect the transfer of nutrients and oxygen to the fetus either damaging the placenta or decreasing the placental blood flow.

Finally, conditions of increased plasma levels of cholesterol and triglycerides have been linked to increased fatty

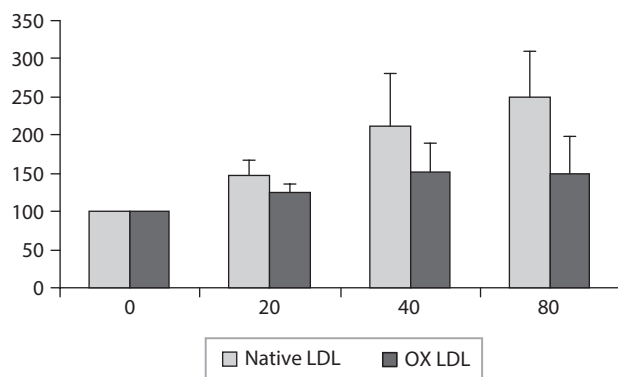


Figure 4.3 Progesterone secretion in trophoblast incubated with increasing concentrations of normal or oxidized low-density lipoprotein (for details, see reference 52).

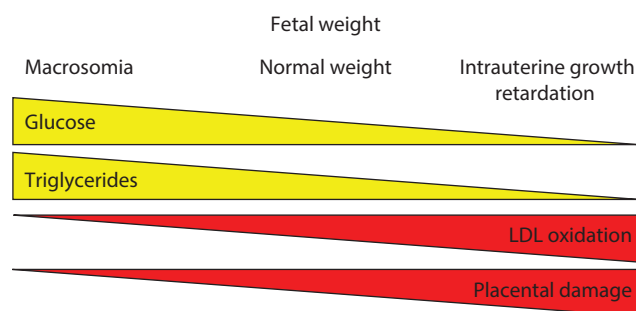


Figure 4.4 Potential factors affecting fetal growth in pregnancies complicated by gestational diabetes mellitus. Factors increasing fetal growth are shown in yellow and conditions decreasing fetal growth in red.

streaks in the fetal arteries.^{60,61} As a consequence, children from GDM pregnancies may have a higher incidence of these alterations than newborns from normal pregnancies. Further studies are needed to demonstrate if stillborns from GDM pregnancies also have increased incidence of fatty streaks in their arteries.

To sum up, in GDM, there is a combination of factors that may affect the nutrient supply to the fetus (Figure 4.4). Under certain conditions, increased supply of glucose and triglycerides toward the fetus may lead to increased fetal growth and macrosomia. Nevertheless, under certain conditions, dyslipidemia and hyperglycemia found in GDM may lead to increased LDL oxidation, placental damage, and vascular dysfunction; such a condition would decrease the transfer of nutrients toward the fetus and lead to intrauterine growth retardation (Figure 4.4). At present, most efforts are directed toward blood glucose normalization, and little attention has been paid to the dyslipidemia and to the LDL oxidation associated with this process; in fact in our institution, in GDM pregnancies with optimal metabolic control, we have found a higher incidence of intrauterine growth retardation (13.5%) than macrosomic infants (9.1%).⁴⁹ Further studies are needed to obtain a better understanding of the role of dyslipidemia in the maternal and fetal complications associated with GDM. There is a need of studies to determine why some pregnancies complicated by GDM causes intrauterine growth retardation instead of large infants.

Amino acid alterations in pregnancies complicated by gestational diabetes

In GDM, there is an increase in the number of essential and nonessential amino acids in umbilical venous and arterial concentration,⁶² compared to the values found in normal pregnancies. The higher plasma levels of fetal amino acids do not seem to be related to a higher concentration in maternal plasma, as only ornithine has been shown to increase in plasma from pregnant women with GDM.⁶² More recently, studies analyzing maternal protein and amino acid metabolism by stable isotope methodologies did not find significant differences in either treated⁶³ or untreated GDM^{64,65}

compared to normal pregnancies. However, the elevation observed in the plasma amino acid concentration in the umbilical cord, but not in maternal circulation, suggests that placental amino acid exchange and/or fetal-placental metabolism is altered in GDM.⁶²

Studies in vitro show that among the different amino acid transporters, the expression of system A, which mediates the transfer of neutral amino acids such as alanine, serine, and glutamine, is increased in diabetic pregnancies.^{66,67} This, in turn, could increase the uptake and delivery of neutral amino acids into the fetus. However, it does not seem to be the primary cause of accelerated fetal growth. Other transporters such as the specific system for leucine (system L) have also been shown to be increased in microvillous plasma membranes isolated from GDM pregnancies with large babies for their gestational age.^{66,67} Nevertheless, other authors did not find an increased activity of these transporters.⁶⁸ It is remarkable that leucine has been proven to be an effective stimulus for fetal insulin secretion in human pancreas studied in vitro.⁶⁹ In vivo studies applying stable isotope techniques have provided evidence to suggest that leucine,

taken up across the microvillous plasma membranes, is rapidly transferred to the fetus, contributing to the accelerated fetal growth in these patients.^{66,67} More studies are needed for a further clarification of the role of amino acid metabolic alterations associated with GDM.

In conclusion, GDM is a condition of increased maternal metabolic fuels; such a condition in the majority of pregnancies leads to a higher fetal growth, although under certain conditions, the increased fuels, mainly lipids, through oxidative process and increased free radical generation may lead to placental and vascular damage, compromising the normal development of pregnancy and fetal growth.

Acknowledgments

I dedicate this chapter to my former mentor, Bob Knopp, who introduced me to the world of pregnancy and lipids, but most importantly taught me with his example how to take care of patients in a loving and compassionate way (B. Bonet).

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5 Nutrient delivery and metabolism in the fetus

William W. Hay, Jr., Paul J. Rozance, Stephanie R. Wesolowski, and Laura D. Brown

Introduction

Fetuses of diabetic mothers have markedly different growth rates and develop considerably different body compositions despite all having a mother with diabetes mellitus during her pregnancy. Fetuses of poorly controlled diabetics who have wide swings in meal-associated plasma concentrations of glucose and fatty acids tend to be macrosomic, with large amounts of subcutaneous adipose tissue. Such conditions are most commonly associated with gestational diabetics. In contrast, severely diabetic pregnant women, particularly those with vascular disorders and hypertension, frequently produce smaller placentas that transfer fewer nutrients to the fetus; their fetuses tend to be growth restricted and relatively devoid of skeletal muscle and body fat. To appreciate how such disparate patterns of growth can occur, it is important to understand the basic aspects of nutrient transport to the fetus. In the following discussion, data from a variety of animal models, principally sheep, are used to augment and support the more limited information from humans.

Nutrients for the fetus

The principal metabolic nutrients in the fetus are glucose and amino acids. Glucose (including its metabolic product lactate, which is produced primarily in the placenta) serves as the principal substrate in the fetus for maintenance energy production and expenditure, energy storage in glycogen and adipose tissue, and the energy requirements of protein synthesis and growth. Amino acids, while primarily providing the structural basis for protein synthesis and growth, also serve as oxidative substrates for energy production, particularly when glucose supply is restricted. Fatty acids also are taken up by the fetus, where they are primarily used for structural components of membranes and for growth of adipose tissue. In humans, fatty acid oxidation occurs readily after birth, even in

preterm infants, indicating that the lack of marked fatty acid oxidation in the fetus is primarily due to the ready supply and oxidation of glucose, lactate, and amino acids, as well as the limited amounts of enzymes and transporters in fetal tissues necessary to deliver fatty acids into the mitochondria. Hormonal regulation of metabolic substrate utilization and growth in the fetus, including the effects of insulin and the insulin-like growth factors (IGFs), is important but secondary to the supply of nutrient substrates.¹⁻⁴

Role of the placenta in nutrient transfer to the fetus

The placenta plays a key role in nutrient transfer to the fetus. The placenta contains membrane transporter proteins for glucose, lactate, and fatty acids that facilitate their transport to the fetus by concentration gradients. The placenta also actively concentrates amino acids in the trophoblast cells of the placenta and then transfers the amino acids to the fetal plasma, processes aided by the unique positioning of specific amino acid transporter proteins and systems on the maternal-facing and fetal-facing trophoblast membranes. The placenta also consumes nutrient substrates at a very high metabolic rate, producing part of the transplacental nutrient substrate gradient for glucose and fatty acids, as well as specific metabolic products of glucose, lipid, and amino acid metabolism that then provide a unique fetal plasma nutrient milieu. This creates a unique placental-fetal metabolic interaction, in which certain substrates transported directly to the fetus by the placenta are then metabolized into products for both fetal and, in turn, placental metabolism. Collectively, these nutrient metabolic and transport processes provide a unique fetal nutrient metabolic milieu that supports the essential tissue and organ-specific metabolic pathways necessary for the high growth rate and rapidly changing development of the fetus.¹⁻⁴

Nutrient supply and fetal metabolic rate

Estimates of carbon supply to the fetus are compared with requirements for energy production and storage in Table 5.1. The fetal glucose/oxygen metabolic quotient, an index of that fraction of fetal oxygen consumption that could be accounted for by complete oxidation of net fetal glucose uptake from the placenta, is <1.0 .⁴ Furthermore, the fraction of fetal glucose utilization that actually produces CO_2 is only *c.* 0.5–0.6 (Table 5.2).^{5–7} Thus, carbon substrates other than glucose are metabolized to meet the oxidative requirements imposed by the rate of fetal oxygen consumption; as noted earlier, these include lactate and amino acids principally, given the limited evidence for

fatty acid oxidation in the fetus. At markedly reduced rates of glucose supply to the fetus, fetal glucose utilization rates (GUR) decrease proportionally, until about 50% of normal GUR, when GUR is maintained by the development of glucose production, initially glycogenolysis, but then also gluconeogenesis.^{8,9} Fetal oxygen consumption remains near normal under such conditions of reduced nutrient supply from the placenta, indicating an increase in the reciprocal oxidation of other substrates, such as glucose released from glycogen and gluconeogenesis from amino acids. Simultaneously, there is an associated decrease in fetal protein accretion rates, which limits the requirement for energy substrates to maintain protein synthesis and net protein balance.¹⁰

Table 5.1 Estimated human fetal nutrient substrate balance in late gestation

	Carbon (g/kg/day)	Calories (kcal/kg/day)
<i>Requirement</i>		
Accretion in carcass: nonfat (human)	3.2	32
Accretion in carcass: fat (human)	3.5	33
Excretion as CO_2	4.4	0
Excretion as urea	0.2	2
Excretion as glutamate	0.3	2
Heat (measured as O_2 consumption)	0.0	50
Total	11.6	119
<i>Uptake</i>		
Amino acids	3.9	45
Glucose	3.7	26
Lactate	1.7	21
Fatty acids	1.1–2.2	17–34
Total	10.4–11.5	109–126
<i>Sources:</i> Reprinted from <i>An Introduction to Fetal Physiology</i> , Battaglia, F.C. and Meschia, G., Copyright 1986, with permission from Elsevier; Reprinted from <i>Fetal and Neonatal Physiology</i> , 4th ed., Hay, W.W., Jr., Brown, L.D., and Regnault, T.R.H., Fetal requirements and placental transfer of nitrogenous compounds, pp. 585–602, Copyright 2011, with permission from Elsevier; Sparks, J.W. et al., <i>J. Clin. Invest.</i> , 70, 179, 1982.		

Table 5.2 Fetal carbon substrate oxidation in relation to fetal oxygen consumption (VO_2)^a

Substrate	Oxidation fraction	Carbon for oxidation	
		(mmol/min/kg)	Fraction of fetal VO_2
Glucose	0.55	0.09	0.29
Lactate	0.72	0.14	0.50
Amino acids	0.30	0.03	0.09
Total			0.88
<i>Sources:</i> Reprinted from <i>Fetal and Neonatal Physiology</i> , 4th ed., Hay, W.W., Jr., Brown, L.D., and Regnault, T.R.H., Fetal requirements and placental transfer of nitrogenous compounds, pp. 585–602, Copyright 2011, with permission from Elsevier; Hay, W.W., Jr. et al., <i>Am. J. Physiol.</i> , 256, E704, 1989; DiGiacomo, J.E. and Hay, W.W., Jr., <i>Metabolism</i> , 39, 193, 1990; Sparks, J.W. et al., <i>J. Clin. Invest.</i> , 70, 179, 1982.			
^a Estimates derived from data in fetal sheep in late gestation.			

Similar to nutrient deprivation, excess delivery of nutrients to the fetus, such as with experimental glucose infusion into the fetus or mother, decreases amino acid oxidation, but has little effect on fetal metabolic rate. A maximal increase of c. 15% has been observed in fetal sheep infused directly with glucose and insulin.⁷ The balance of excess glucose consumption under these conditions maximizes glycogen stores, and in those fetuses that can produce abundant fat, such as the human, augments the growth of adipose tissue. Excess fetal amino acids are used primarily for oxidation, substituting their carbon for that of glucose and lipids, and not excess growth of lean body mass.^{11–13} Thus, fetuses of diabetic mothers tend primarily to be macrosomic (i.e., obese) due to increased storage of glucose and lipids as fat in adipose tissue without increased oxidation of these maternally derived fuels/substrates. Similarly, excess insulin in the presence of excess amino acids has been shown in fetal sheep to produce the same linear growth rate with only minimally increased production of lean mass as occurs with normal insulin concentrations and amino acid supplies.^{14,15}

Fetal carbohydrate supply and metabolism

The rate of glucose transfer from maternal to fetal plasma and the net rate of fetal glucose uptake are directly related to the maternal glucose concentration (Figure 5.1a).¹⁶ Fetal growth rate, glycogen deposition, and fat production and

storage in adipose tissue also are directly related to fetal glucose supply and uptake. Thus, it is not surprising that fetuses of hyperglycemic, diabetic mothers tend to contain maximal amounts of hepatic and muscle glycogen and excess body fat than do fetuses of more normally glycemic mothers, whether they are diabetic or not.^{17–20}

The concentration of glucose in the fetal plasma declines relative to that in the maternal plasma over the second half of gestation. This increases the transplacental glucose concentration gradient in later gestation, providing a greater driving force to supply glucose for the increasing glucose requirements of the growing fetus.²¹ The decrease in fetal glucose concentration over the second half of gestation represents an absolute increase in glucose clearance by the fetus. At least three principal mechanisms are responsible for this increase in glucose clearance: The size, cellularity, and glucose metabolic rate of the brain increase relative to other fetal tissues and organs; there is progressive development of fetal insulin secretion by the expanding mass of pancreatic islets and beta cells; and there is increased growth of insulin-sensitive tissues, primarily skeletal muscle, and also the heart and adipose tissue.

Placental glucose transport

Glucose transporters

Placental glucose uptake and transfer are mediated by Na⁺-dependent transport systems on both the maternal-facing microvillus and fetal-facing basal plasma membranes of the

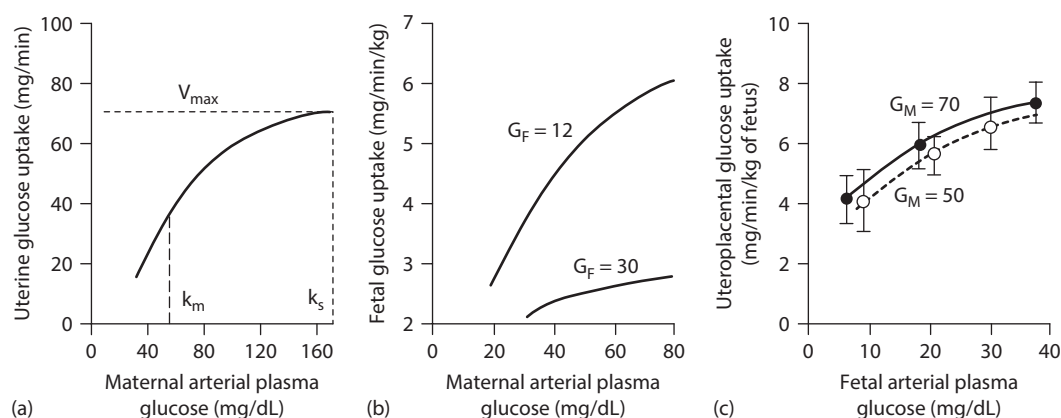


Figure 5.1 (a) Schematic representation of the effect of maternal glucose concentration on uterine glucose uptake, based on experiments in which glucose was infused into pregnant sheep after an overnight fast to produce a large variety of maternal arterial blood glucose concentrations. Fick principle measurements were then made of net uterine glucose uptake rates versus the maternal arterial blood glucose concentration, which shows saturation kinetics with an approximate k_m value in the physiological range of maternal glucose concentration (about 50–60 mg/dL). (b) Fetal glucose uptake (net transfer of glucose from placenta to fetal circulation) plotted versus maternal arterial glucose concentration, showing a saturable dependence of fetal glucose uptake on maternal glucose concentration. In addition, this relationship is left-shifted as fetal glucose concentration is decreased, showing that as fetal glucose concentration is decreased relative to that of the mother, which increases the maternal–fetal glucose concentration gradient, placental-to-fetal glucose transfer increases. (c) Net rate of uteroplacental glucose consumption in sheep, expressed per kilogram of fetus, plotted versus fetal arterial plasma glucose. Solid line: values measured while maternal arterial plasma glucose was clamped at about 70 mg/dL. Dotted line: values measured while maternal arterial plasma glucose was clamped at about 50 mg/dL. These data show that although maternal glucose concentration determines glucose entry into the uteroplacenta and fetus, actual uteroplacental glucose consumption is regulated largely by the fetal glucose concentration. (Reproduced from Hay, W.W. Jr., Placental function, in: Gluckman, P.D. and Heymann, M.A., eds., *Pediatrics and Perinatology: The Scientific Basis*, 2nd ed., Edward Arnold, London, U.K., 1996, pp. 213–227. With permission; [a] Adapted from data in Hay, W.W. Jr. and Mezmarich, H.K., *Proc. Soc. Exp. Biol. Med.*, 190, 63, 1988; [b and c] Adapted from data in Hay, W.W. Jr. et al., *Am. J. Physiol.*, 258, R569, 1990.)

syncytiotrophoblast.²² The predominant molecular isoforms of glucose transporters (GLUT) in the placenta are GLUT1 and GLUT3,²³ although GLUT8 also has been found in the placenta and in sheep is reduced in amount with intrauterine growth restriction (IUGR),²⁴ as has GLUT9, both isoforms of which appear to be increased in diabetic pregnancies.²⁵ Participation of GLUT3 in glucose uptake and transport has not been confirmed *in vivo* in the human placenta, although in sheep placenta, cytochalasin binding assays indicate that GLUT3 might account for as much as 40% of glucose uptake by the end of gestation.²⁶ Other studies in sheep indicate that GLUT3 is localized close to mitochondria where it might serve to support placental glucose uptake and energy production at low glucose concentrations, thus preserving placental function.²⁷ In other studies in human placental tissue, GLUT3 appears to peak earlier in gestation and declines toward term.²⁸ GLUT3 also regulates intraplacental glucose transport that, in mice, at least, appears reciprocally related to leucine transport.²⁹ Studies in human placentas indicate that GLUT3 is upregulated with intrauterine growth restriction,³⁰ as also found with the original classical studies of placental hypoxia *in vitro*.³¹ Further studies are indicated in diabetic pregnancies, as there is evidence that fetal macrosomia is associated with increased expression of GLUT3.³²

In vivo studies of human placentas from high-altitude hypoxia with IUGR indicate reduced GLUT1 expression.³³ With GLUT3 upregulated under similar conditions, this would set the stage for enhanced placental glucose consumption but reduced glucose supply to the fetus, perhaps contributing to fetal growth restriction. Other studies have noted that corticotropin-releasing hormone (CRH) also affects GLUT1 (increases) and GLUT3 (decreases) via specific receptors in trophoblast cells, though physiological significance of these changes has not been determined.³⁴ Related to the effects of CRH, both GLUT1 and GLUT3 are downregulated by glucocorticoids, perhaps playing a role in how maternal stress can lead to placental insufficiency and intrauterine growth restriction.³⁵ Still other studies have amplified the impact of placental GLUT1 and GLUT3 regulation by systemic hormones. For example, one study noted that maternal growth hormone treatment increases fetal growth, in part, by enhancing placental nutrient transporter protein expression and hence fetal nutrient supply, as well as trophoblast proliferation and differentiation, and may have the potential to ameliorate intrauterine growth restriction.³⁶

Despite considerable study, the regulation of placental GLUT expression and activity remain poorly defined. Placental GLUT1 is acutely upregulated by hypoxia and hyperglycemia and downregulated by hypoglycemia,^{37,38} while hypoglycemia leads to downregulation, although one study found upregulation of GLUT1 in the growth-restricted rat placenta.³⁹ Chronic changes in glycemia generally are associated with diminished expression and glucose transport.⁴⁰ *In vitro* studies indicate that changes in GLUT concentrations are related to transport capacity, but this has not been demonstrated *in vivo*, except in experiments in which the transporters were competitively blocked by pharmacologic inhibitors. A recent study in mice also indicates that

IGF-1 can upregulate GLUT1, GLUT3, GLUT8, and GLUT9 sufficiently to correct some aspects of placental insufficiency and reduced placental glucose uptake and transport.⁴¹ Increasing maternal feed intake to meet calculated energy requirements in previously nutrient-restricted ewes during the second half of gestation increases placental mass and fetal weight and the abundance of GLUT1, an adaptation not observed if maternal food intake is increased above requirements,⁴² the opposite of what occurs with nutrient restriction that results in IUGR—inhibition of placental mammalian target of rapamycin (mTOR) and insulin/IGF-1 signaling resulting in downregulation of placental nutrient transporters may link maternal undernutrition to restricted fetal growth.⁴³

Kinetics of glucose uptake and transport by the placenta

Although the effect of the maternal glucose concentration on net placental-to-fetal glucose transfer demonstrates saturation kinetics,¹⁶ this relationship does not necessarily define the quantitative characteristics of placental-to-fetal glucose transport capacity, because as maternal glucose concentration and placental glucose transport are increased, both fetal glucose concentration and fetal GUR increase. Other studies in which glucose was infused directly into the fetus have shown degrees of increase (slope) and saturation of fetal GUR occurring at about the same fetal glucose concentrations as determined by maternal glucose infusions.⁴⁴ Thus, the maternal glucose infusion approach reflects fetal glucose consumption kinetics as well as those of placental-to-fetal glucose transfer. To address this experimental problem, different studies have used glucose clamp procedures to regulate the maternal-to-fetal glucose concentration gradient at different maternal and fetal glucose concentrations.⁴⁵ As shown in Figure 5.1b, placental-to-fetal glucose transfer is sensitive to a change in fetal glucose concentration and thus the maternal-to-fetal glucose concentration gradient, regardless of the maternal glucose level.⁴⁶

At almost any maternal glucose concentration, therefore uteroplacental glucose consumption rate (the metabolism of glucose by the uteroplacenta) is directly related to the fetal glucose concentration (Figure 5.1c). In fact, when the transplacental glucose concentration is abolished, *c.* 75% of the glucose consumed by the uteroplacenta is supplied by the fetal circulation.⁴⁷ These observations imply that the fetal side of the uteroplacenta is markedly more permeable to glucose than the maternal side. They also indicate that changes in fetal glucose concentration have a strong influence on placental glucose flux and metabolism. The importance of this regulation of placental-to-fetal glucose transfer and net uteroplacental glucose consumption by fetal glucose concentration is highlighted by observations in chronically hypoglycemic pregnant sheep in which fetal glucogenesis developed.⁸ Fetal glucose production contributes glucose molecules to the fetal glucose pool and appears to be sufficient in amount to sustain fetal glucose utilization at near-normal rates. As a result, the placental-to-fetal glucose concentration gradient and the placental-to-fetal glucose transfer rate are relatively reduced; under these

Table 5.3 Metabolic rates in the fetus that account for glucose utilization^a

	Glucose utilization rate (mg/min/kg fetus)	Percent of total
Whole fetus (sheep, measured)	5.0	100
Whole fetus (human, estimated)	6.0–8.0	100
Brain (sheep, measured)	0.8	16
Brain (human, estimated)	4.0	50–67
Heart (sheep, measured)	0.65	13
Lungs (sheep, estimated)	0.1	2
Liver (sheep, measured)	0.1	2
Red blood cells (human, estimated)	0.1	2
Gut (sheep, estimated)	unknown	unknown
Carcass/skeletal muscle (estimated, sheep)	3.25	65
Total of organs accounted for		
Sheep	5.0	100
Human	8.2	103–137

Sources: Reprinted from *An Introduction to Fetal Physiology*, Battaglia, F.C. and Meschia, G., Copyright 1986, with permission from Elsevier; Reprinted from *Fetal and Neonatal Physiology*, 4th ed., Hay, W.W., Jr., Brown, L.D., and Regnault, T.R.H., Fetal requirements and placental transfer of nitrogenous compounds, pp. 585–602, Copyright 2011, with permission from Elsevier; Sparks, J.W. et al., *J. Clin. Invest.*, 70, 179, 1982.

^a Based on data in fetal sheep and estimates for human fetuses for the brain.

circumstances, uteroplacental glucose consumption is maintained at near-normal rates for the level of maternal glycemia. Fetal glucose production can compensate for a reduced maternal glucose supply and sustain placental as well as fetal glucose utilization requirements.

Gestational changes in placental glucose transfer

Placental glucose transport increases markedly over gestation. In sheep, the increase in transport capacity accounts for *c.* 60% of the increase in placental glucose transport, with an increase in the transplacental glucose concentration gradient accounting for the remaining 40%.⁴⁷ This increased transport capacity most likely reflects the growth of the surface area of the trophoblast and increased numbers of GLUT.^{26,37} It has not been determined if an increase in trophoblast membrane GLUT concentration occurs as well. The regulation of this developmental increase in GLUT abundance, other than by remodeling of the trophoblast membrane surface area, remains unknown.

Fetal glucose uptake and utilization

GUR in near-term fetal sheep is *c.* 5–7 mg/min/kg.⁴⁸ This value is similar to those measured in term human newborn infants using stable isotope tracer methodology⁴⁹ and is about half the value that occurs at midgestation in fetal sheep¹⁶ when fetal growth, protein turnover rate, and fractional protein synthetic rates also are about twice those closer to term. The high correlation between fetal glucose utilization and growth rates indicates that glucose probably serves a major role as the energy supply for the protein synthesis required for growth. Indeed, fetal growth restriction

is directly related to glucose deprivation.⁵⁰ Table 5.3 presents estimated utilization rates of glucose in several fetal organs and the remaining carcass of fetal sheep in late gestation. All organs are dependent on the plasma glucose concentration for their specific rate of glucose uptake, while the skeletal muscle, heart, and liver develop insulin sensitivity in later gestation. The acute effect of increased fetal plasma insulin concentrations results in increased fetal glucose utilization and decreased fetal plasma glucose concentrations.⁷ It still is not known to what extent basal insulin concentration affects glucose uptake by specific organs and tissues in the fetus. However, an acute decrease in the fetal plasma insulin concentration, such as by somatostatin infusion (studies in fetal sheep), does not affect measurements of the fetal GUR. These procedures do, however, lead to an increase in the fetal glucose concentration,⁵¹ which may be a consequence of decreased glucose disposal or increased glucose production. Thus, the basal plasma insulin concentration in the fetus appears to regulate glucose production but not utilization; the latter is more under the control of the plasma glucose concentration.

A chronic decrease of fetal plasma insulin concentration, however, either by pancreatectomy or streptozotocin injection (a drug that leads to destruction of the pancreatic beta cells) into the fetus,^{52–54} results in an increased fetal plasma glucose concentration and decreased glucose utilization.⁵⁵ As discussed previously, fetal hyperglycemia decreases placental-to-fetal glucose transfer. Chronic hyperglycemia in fetal sheep also is associated with decreased peripheral tissue insulin sensitivity and glucose utilization capacity,⁵⁶ as well as the potential release of insulin's normal inhibition of hepatic glucose production. Examples of metabolic effects of increased glucose supply to the fetus are shown in Table 5.4.¹

Table 5.4 Fetal responses to increased glucose supply*Acute: mild-moderate*

Increased glucose uptake
 Increased insulin production and secretion
 Hyperinsulinemia
 Increased glucose utilization
 Increased fetal oxygen consumption
 Mild arterial hypoxemia
 Respiratory acidosis
 Increased placental lactate production
 Increased fetal lactate uptake and utilization

Acute: severe

Arterial hypoxemia
 Hypoinsulinemia
 Increased erythropoietin
 Increased fetal oxygen consumption
 Metabolic acidosis
 Decreased placental perfusion
 Fetal demise

Chronic

Decreased insulin secretion and/or synthesis
 Decreased peripheral insulin sensitivity
 Increased ratio of placental glucose consumption to placental glucose transfer

Source: Reproduced from Hay, W.W., Jr. et al., Nutrition and development of the fetus: Carbohydrate and lipid metabolism, in: Duggan, C.P., Watkins, J.B., Koletzko, B., and Walker, W.A., eds., *Nutrition in Pediatrics: Basic Science and Clinical Applications*, 5th ed., PMPH-USA, Ltd., Shelton, CT, in press, 2015, Chapter 28.

As a result of chronic fetal glucose deprivation, from whatever cause, fetal growth rate diminishes and insulin concentrations are reduced. However, fetuses from placental insufficiency have increased basal and insulin-stimulated GUR.^{57,58} In these fetuses, acute insulin has little effect on protein metabolism.¹² These results indicate that the predominant growth-regulating effect of insulin in the fetus is its capacity to enhance glucose utilization rather than protein metabolism. Furthermore, tissues in the growth-restricted fetus may have differences in insulin sensitivity in late gestation, with peripheral tissues remaining insulin sensitive for glucose disposal and the liver becoming insulin resistant to suppression of glucose production.^{57,58}

Fetal glucose transporters

GLUT1 is found throughout the fetal tissues and on all endothelial cells and probably accounts for the majority of basal tissue glucose uptake from the fetal plasma. GLUT4 is found in the heart, adipose tissue, and skeletal muscle. In the fetal sheep, GLUT1 protein concentration

is upregulated by hypoglycemia and hypoinsulinemia in skeletal muscle and adipose tissue, while there is no change in the brain. In contrast, hyperglycemia appears to downregulate GLUT1 protein concentrations in most tissues.^{37,59} Insulin-responsive GLUT4 protein is upregulated by hypoglycemia,³⁷ but in response to hyperglycemia, it is initially upregulated and then downregulated toward normal, or to less than normal, levels in skeletal muscle and adipose tissue.^{59,60} Acute hyperinsulinemia decreases fetal glucose concentrations and increases whole fetal GUR,⁸ but it has been difficult to demonstrate in which organs this increased GUR takes place. Hyperinsulinemia also appears to have acute effects on increasing protein concentrations for both GLUT1 and GLUT4.^{59,60} In humans, there is considerable evidence for insulin lowering the plasma glucose concentration in the preterm and term newborn. The principal action of insulin in the human fetus is uncertain, but a unique effect, due to fatty acid supplies, is to promote lipid formation and deposition in adipose tissue. In this situation, substrate supply (glucose, fatty acids, triglycerides, and glycerol) probably is as or more important than insulin itself. Different studies among species, tissues studied, gestational ages, and conditions of glycemia and insulinemia show considerable variability and complexity of changes in GLUT concentrations during fetal life.

Kinetics of the glucose utilization rate in the fetus

The capacity for glucose utilization in the human fetus can only be estimated from measurements in infants born preterm or in animal models such as the sheep. In preterm humans, doubling or even tripling of GUR from basal is possible.⁶¹ This GUR capacity is variable, however, as increased entry of glucose into the fetal plasma from the placenta increases fetal glucose concentration and insulin secretion, which, in turn, augment fetal glucose utilization, thus limiting further increases in fetal glucose concentration. Glucose and insulin clamp experiments in fetal sheep, in which glucose or insulin or both are infused until GUR reaches maximal rates, have shown that plasma glucose and insulin concentrations act independently (i.e., additively) to increase glucose utilization and oxidation.⁸ Furthermore, while both glucose and insulin enhance fetal GUR according to saturation kinetics, it is not known how this effect is partitioned among different fetal organs. Despite wide changes in glucose utilization, the relative proportion of glucose oxidized during short-term 3- to 4-hour studies—c. 55%—does not change significantly over the entire range of glucose utilized. Furthermore, because oxygen consumption, and thus the fetal metabolic rate, does not vary significantly, if at all, under these circumstances, oxidation of other carbon substrates, such as amino acids and lactate, must increase in compensation. Indeed, acute hypoglycemia in fetal sheep leads to a near doubling of the rate of leucine oxidation relative to the rate of leucine disposal from the plasma.⁶² In the human fetus, glucose and/or insulin may promote lipogenesis more than oxidation. This may occur because the human fetus naturally produces adipose

tissue in late gestation, similar to adult humans in whom higher rates of glucose utilization are partitioned more into glucose storage in adipose tissue fat than into oxidation. Glucose carbon also contributes significantly to the formation of glycogen, which is stored primarily in skeletal muscle, but also in the heart, liver, and lung, and to the carbon contained in amino acids and synthesized proteins.

Fetal insulin secretion

Glucose-stimulated fetal insulin secretion (measured as an acute increase in fetal plasma insulin concentration) increases more than fivefold during the second half of gestation in fetal sheep and has been documented in third-trimester human fetuses.^{63,64} Fetal insulin secretion can be modified by the degree, duration, and pattern of changes in the fetal plasma glucose concentration. Sustained, marked, relatively constant hyperglycemia actually decreases fetal insulin secretion, while pulsatile hyperglycemia increases fetal insulin secretion and fetal β -cells.^{56,65–68} This is consistent with findings in gestational diabetic women in whom there is a strong tendency to develop increasingly exaggerated, meal-associated hyperglycemia in late gestation and associated increases in newborn insulin secretion.⁶⁹ Thus, a principal cause of enhanced fetal insulin secretion is variability in the magnitude and the intermittent nature of fetal glucose concentration. Fatty acids also stimulate fetal insulin secretion; their concentrations are increased in pregnant diabetics and in their fetuses in late gestation, perhaps contributing to augmented insulin secretion.⁶⁶ Chronic hypoglycemia diminishes fetal insulin secretion and β -cell mass.⁷⁰ Increased amino acid supply augments, and decreased amino acid supply attenuates, fetal insulin secretion.^{71,72}

Effect of other hormones on fetal glucose metabolism

Fetal thyroid hormone indirectly enhances fetal glucose utilization by increasing the fetal metabolic rate (oxygen consumption).⁷³ Changes in fetal plasma cortisol concentrations during late gestation have little effect on fetal glucose concentrations or on the rates of glucose utilization.⁷⁴ However, fetal plasma cortisol concentrations do increase in very late gestation, at which time cortisol-dependent increases in fetal hepatic glycogenolytic and gluconeogenic enzyme activities develop. These may enhance the glucogenic capacity of the fetus, thereby contributing to the endogenous glucose production observed in normal fetuses just before term and at the time of delivery.⁷⁵ Glucagon and circulating catecholamines (adrenal epinephrine and spillover norepinephrine from peripheral nerve endings) are normally present in modest concentrations in the fetal plasma, but they do stimulate fetal glucogenesis when infused into the fetus. Catecholamines promote glucose production at physiological levels,⁷⁶ but glucagon must reach relatively high concentrations in the fetal plasma to do this.⁷⁷

Insulin, IGF, and other growth factors

Glucose acts at the transcriptional level to regulate the synthesis and thus plasma concentrations of both IGF-1 and IGF-2.^{78,79} Conversely, infusion of IGF-1 into late-gestation fetal sheep promotes both glucose and amino acid utilization.⁷⁹ In turn, increased fetal plasma IGF-1 concentrations have been shown to either inhibit fetal protein breakdown⁸⁰ or promote fetal protein synthesis and accretion,⁷⁹ depending on the availability of circulating amino acids. These observations indicate that IGF-1 indirectly enhances the capacity for glucose to promote the fetal nitrogen balance and growth.⁸¹ Likewise, acutely increased insulin concentrations in fetal sheep promote glucose utilization, amino acid utilization, and net nitrogen balance,^{82,83} as well as activate proteins in the mitogen-activated protein (MAP) kinase cascade.⁸⁴ Such effects are probably short-lived, as chronically raising fetal insulin concentrations above normal does not increase fetal growth beyond normal rates.¹⁵

Fetal glucose carbon contribution to glycogen formation

Many fetal tissues, including the placenta, as well as the brain, liver, lung, heart, and skeletal muscle, produce glycogen over the second half of gestation.⁸⁵ Liver glycogen content increases with gestational age (Figure 5.2) and is the most important store of glycogen for systemic glucose needs, because only the liver contains sufficient glucose-6-phosphatase for the release of glucose into the circulation.⁸⁶ Skeletal muscle glycogen content increases during late gestation, whereas lung glycogen content decreases with loss of glycogen-containing alveolar epithelium, development of type II pneumocytes, and onset of surfactant production.⁸⁷ Cardiac glycogen concentrations decrease with gestation as cellular hypertrophy develops. Despite this decrease, the cardiac glycogen content is essential for postnatal cardiac energy supply and cellular function; in fact, deficits of cardiac glycogen are associated with shortened survival time during periods of anoxia.⁸⁷ Fetal glycogen synthetic rates vary from low, steady rates of accumulation in species with relatively long gestations, such as the human and sheep, to exceptionally high rates in species such as the rat that have relatively short gestations. In larger, more slow-growing fetuses (e.g., sheep, monkey, human), glycogen synthesis by the liver accounts for only a small (<10%) portion of fetal glucose utilization.⁸⁸

Fetal glucogenesis

Tracer studies in humans⁸⁹ and sheep¹⁶ have shown the same specific activity or enrichment ratio of tracer glucose to nonlabeled glucose in fetal as well as in maternal plasma when the tracer glucose is infused into the mother and is transported across the placenta to the fetus. This demonstrates that the only source of glucose in the fetus is from the maternal plasma. Otherwise, new glucose production into the fetal

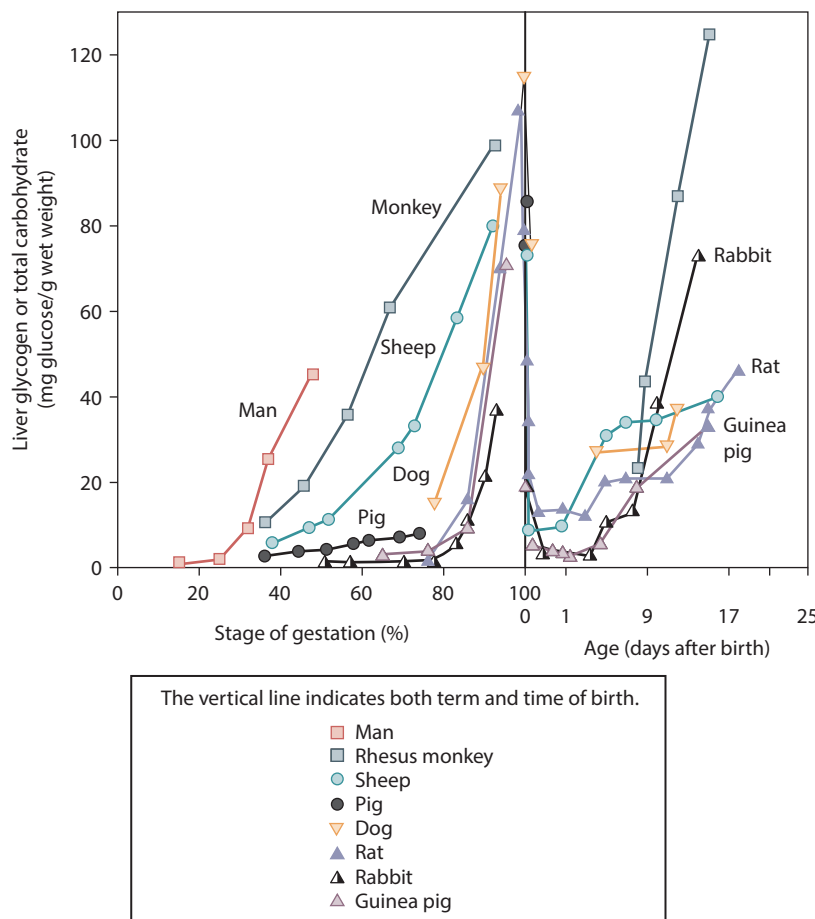


Figure 5.2 Liver glycogen in various species before and after birth. Hepatic glycogen content in several species is shown to increase with gestational age, decrease precipitously during the immediate postnatal period, and increase again with a normal neonatal diet. (From Shelly, H.J., *Br. Med. Bull.*, 17, 137, 1961. With permission.)

plasma either from the fetus itself or from the placenta would dilute the tracer glucose coming from the mother along with unlabeled glucose, thus lowering the fetal labeled glucose-specific activity or enrichment ratio. Furthermore, studies in fetal sheep have shown that the net uptake of glucose by the fetus from the placenta invariably is equal to the fetal GUR, independently measured with glucose tracers.^{48,57,90,91} Thus, there is no evidence for fetal glucose production under normal conditions. Also, there is little if any fetal gluconeogenesis under the conditions of short-term (1–4 hours) changes in maternal and fetal glucose concentrations, placental-to-fetal glucose transfer, and fetal GUR. Measurable rates of fetal glucose production only develop significantly after prolonged periods (several days) of decreased fetal glucose supply and sustained fetal hypoglycemia and hypoinsulinemia.^{51–53,92–94} The capacity of the fetus to make new glucose molecules from nonglucose substrates (e.g., lactate, amino acids, and glycerol) varies considerably among species. In nearly all cases, this appears to be a late gestational development, augmented by hormonal signals including decreased insulin and increased cortisol and catecholamines that activate phosphoenolpyruvate carboxykinase, the rate-limiting step for gluconeogenesis, and glucose-6-phosphatase, the enzyme necessary for the release of glucose from the liver into the circulation.^{54,56}

Fetal lipid metabolism

Placental lipid metabolism and fetal lipid supply

The amount and type of fatty acid or complex lipid transported by the placenta varies among species. Placental lipid transport capacity is greatest in the hemochorial placenta of the human, guinea pig, and rabbit and least in the epitheliochorial placenta of the ruminant and the endotheliochorial placenta of the carnivores.⁹⁵ There are many lipid substances in the plasma that are transported across the placenta that are essential for placental and fetal development, even if they do not contribute to nutritional or energy metabolism. Also, brown fat is common to all fetuses; it is essential for postnatal thermogenesis, even if the neonate is not “fat” with white adipose tissue. Furthermore, many lipid substances entering the fetus are qualitatively different from those taken up by the uterus and uteroplacenta, implying active placental metabolism of individual lipid substances. More complex pathways include lipoprotein dissociation by placental lipoprotein lipase and phospholipase activity.⁹⁶ Maternal plasma triglycerides are hydrolyzed by these enzymes and the released fatty acids are then taken up by the placenta. In the trophoblast cells, the fatty acids are then reesterified and further hydrolyzed, facilitating their diffusion into the fetal

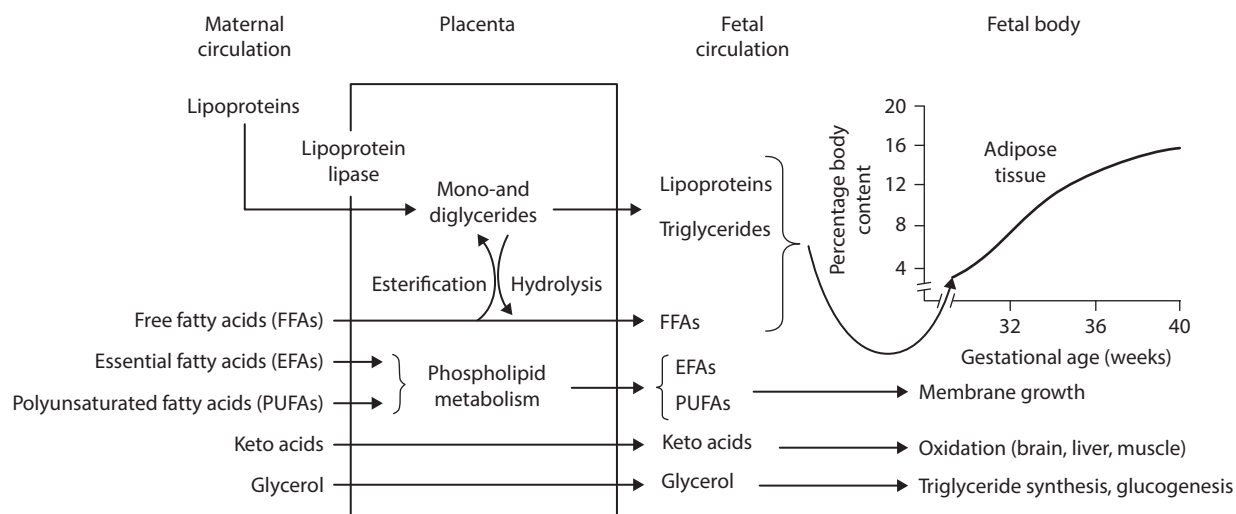


Figure 5.3 Schematic of placental–fetal interrelationships in humans for various aspects of placental lipid metabolism, fetal lipid uptake and metabolism, and fetal lipogenesis into adipose tissue. (Adapted from Hay, W.W., Jr. et al., *Nutrition and development of the fetus: Carbohydrate and lipid metabolism*, in: Duggan, C.P., Watkins, J.B., Koletzko, B., and Walker, W.A., eds., *Nutrition in Pediatrics: Basic Science and Clinical Applications*, 5th ed., PMPH-USA, Ltd., Shelton, CT, 2015 (in press), Chapter 28; Hay, W.W., Jr., *Placenta*, 16, 19, 1995.)

circulation. Triglycerides also are taken up and metabolized by complex processes in the placenta, including metabolic pathways of oxidation, and chain-lengthening, synthesis, and interconversion pathways, followed by release into the fetal plasma as free fatty acids (FFAs) or lipoproteins.⁹⁷ A schema of placental lipid uptake, metabolism, transport, and metabolic interaction with the fetus is shown in Figure 5.3.^{3,97} Recent reviews summarize information about placental lipid transport and fetal lipid metabolism and accumulation.^{98–100}

The most important factor that regulates the flux of lipid into the placenta and into the various pathways of transport and metabolism is the concentration of maternal plasma lipids, including FFAs and triglycerides. For example, placental triglyceride content increases in women who are fasting, who deliver preterm infants, or who have diabetes mellitus—all conditions in which maternal plasma FFA concentrations are increased. Fatty acid transport into the fetal circulation is largely determined by the transplacental gradient of FFAs relative to available circulating binding protein concentrations and the activity and availability of their binding sites. In humans, fetal patterns of essential fatty acids and structural lipids correlate directly with the fatty acid/lipid composition of the maternal plasma (and, indirectly, the maternal diet).^{98–100}

The fetal impact of maternal plasma FFA and lipid concentrations is further reflected in the fetal lipid content and adipose tissue development.¹⁰¹ Fatter (more macrosomic) human fetuses develop in pregnant women who have higher BMIs and plasma glucose, triglyceride, and insulin concentrations, particularly among women with diabetes during pregnancy.¹⁰² Reducing maternal plasma glucose and lipid concentrations with a complex carbohydrate diet also reduces fetal adiposity.¹⁰³ Recent data also indicate that infants from mothers with gestational diabetes mellitus have increased neonatal hepatic fat, which could result

from increased placental lipid transfer or increased de novo lipogenesis fueled by increased insulin and glucose concentrations.¹⁰⁴

In humans, umbilical venous–arterial fatty acid concentration differences in cord blood samples show that the net flux of nonesterified fatty acids into the fetus from the maternal circulation can account for the fetal requirement of fatty acids during the end of pregnancy.¹⁰⁵ Similar estimates in nonhuman primates (e.g., monkey)¹⁰⁶ indicate that in placental fatty acid, transfer across the placenta could account for all fetal fat deposition in late gestation. Overall, therefore, it appears that there is a relatively direct relationship between the permeability of the placenta to lipids, especially fatty acids, and the adiposity of the fetus at term. Human fetuses develop the most body fat, c. 15%–18% of body weight by the end of gestation. Guinea pig and rabbit fetuses whose mothers were fed enriched lab chow are second at c. 12% and c. 7%, respectively. The sheep fetus develops only about 3% body fat by term, because there appears to be practically no fatty acid transfer except for essential fatty acids across the ovine placenta. Other small mammals produce even less fetal body fat content, such as the mouse at only about 1% (Figure 5.4).

Fetal lipid metabolism

Physiological changes that develop in the fetus in late gestation and increase nutrient utilization, such as the increase in plasma insulin concentration, act to enhance net maternal-to-fetal fatty acid and lipid transport by increasing fatty acid utilization in the fetus (largely to develop adipose tissue).¹⁰⁷ Increased utilization of fatty acids by fetal tissues lowers fetal plasma fatty acid concentrations relative to those in the maternal plasma and increases the maternal-to-fetal fatty acid concentration gradients.¹⁰⁸ For example, human maternal venous blood concentrations of fatty acids are directly related to the umbilical artery FFA

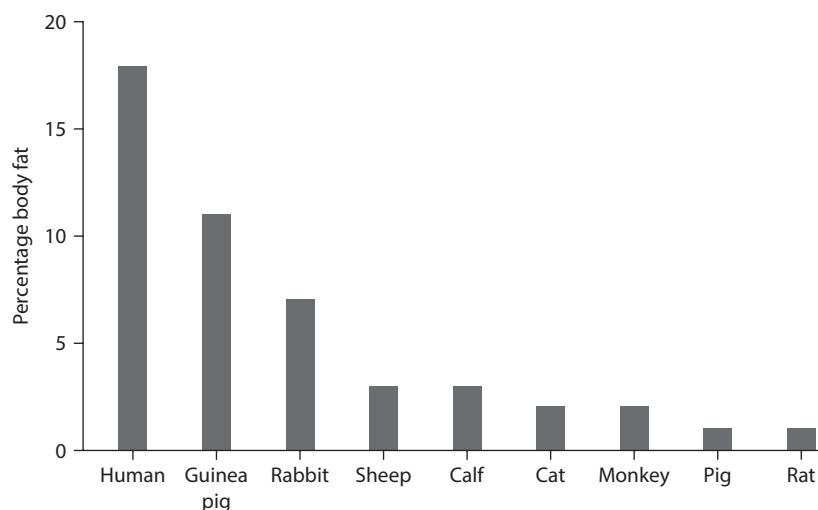


Figure 5.4 Fetal fat content at term as a percent of fetal body weight among species. (Adapted from Hay, W.W., Jr. et al., *Nutrition and development of the fetus: Carbohydrate and lipid metabolism*, in: Duggan, C.P., Watkins, J.B., Koletzko, B., and Walker, W.A., eds., *Nutrition in Pediatrics: Basic Science and Clinical Applications*, 5th ed., PMPH-USA, Ltd., Shelton, CT, 2015 (in press), Chapter 28; Hay, W.W. Jr., *Placenta*, 16, 19, 1995; Reprinted from *An Introduction to Fetal Physiology*, Battaglia, F.C. and Meschia, G., Copyright 1986, with permission from Elsevier.)

concentrations and the umbilical vein–artery concentration differences of FFA.¹⁰⁹

Recent evidence supports the unique roles for leptin in fetal metabolism, including enhancement of growth.¹¹⁰ Umbilical cord leptin concentrations correlate directly with birth weight, and also length and head circumference. They are higher in macrosomic infants of diabetic mothers and lower in infants with IUGR, indicating that the fetal metabolic and hormonal milieu independent of fetal fat content may regulate leptin synthesis and circulating concentrations. Interestingly, cord blood leptin levels also predicted weight gain independent of insulin concentrations over the first 2 years of life. The effect of leptin levels on weight gain was independent of birth weight and was still evident at 24 months. Thus, the wide variation in growth during infancy may be partly regulated by leptin levels present in utero in response to maternal diet and metabolism and by fetal fat accumulation.¹¹¹

Placental amino acid uptake and transport to the fetus

Growth and regulation of placental amino acid transport capacity

In human and in many other species, fetal body weight in late gestation correlates positively with placental weight.¹¹² As pregnancy advances, the increasing protein synthetic and nitrogen balance demands of the growing fetus are met by an appropriate increase in placental size and amino acid transport capacity. This enhanced transport is facilitated by increases in uteroplacental blood flow, trophoblast membrane exchange area, and transporter concentrations in the trophoblast membranes.¹¹³ Fetal growth not only is supported by increased surface area for

exchange, but amino acid transport systems also increase their transport activity over gestation.^{114,115} For example, studies that have evaluated intralitter variation in mice have shown that the lightest placenta of a litter adapts to meet fetal growth demands by increasing surface area for nutrient exchange as well as amino acid transporter activity.¹¹⁵

Several factors regulate the expression and activity of placental amino acid transporters. Insulin, IGF-1, interleukin-6, and tumor necrosis factor- α all have been shown to stimulate placental system A transporter activity,^{117–119} which is the amino acid transporter system responsible for the uptake of small nonessential neutral amino acids. Less is known about the regulation of placental system L transporter activity, which exchanges neutral amino acids for essential amino acids against their concentration gradient, although a recent study of fetal IUGR produced in mice by uterine artery ligation could be reversed in part by IGF-1 gene transfection of the placenta with increased system L activity.¹²⁰ Insulin has been shown to increase system L activity,¹¹⁷ while a 4-day adiponectin infusion into pregnant mice downregulated system L activity and decreased fetal growth.¹²¹ Mechanisms by which these factors regulate amino acid transporter activity are currently being elucidated, though evidence supports the involvement of mTOR and signal transducer and activator of transcription 3 nutrient sensing pathways.^{117,118}

Fetal amino acid uptake

Amino acids are actively concentrated in the trophoblast intracellular matrix by Na⁺/K⁺-adenosine triphosphatase-F- and H⁺-dependent transporter proteins at the maternal-facing microvillous membrane of the trophoblast and then transported into the fetal plasma.¹²² Thus, fetal amino acid concentrations are generally higher than maternal levels.¹²³

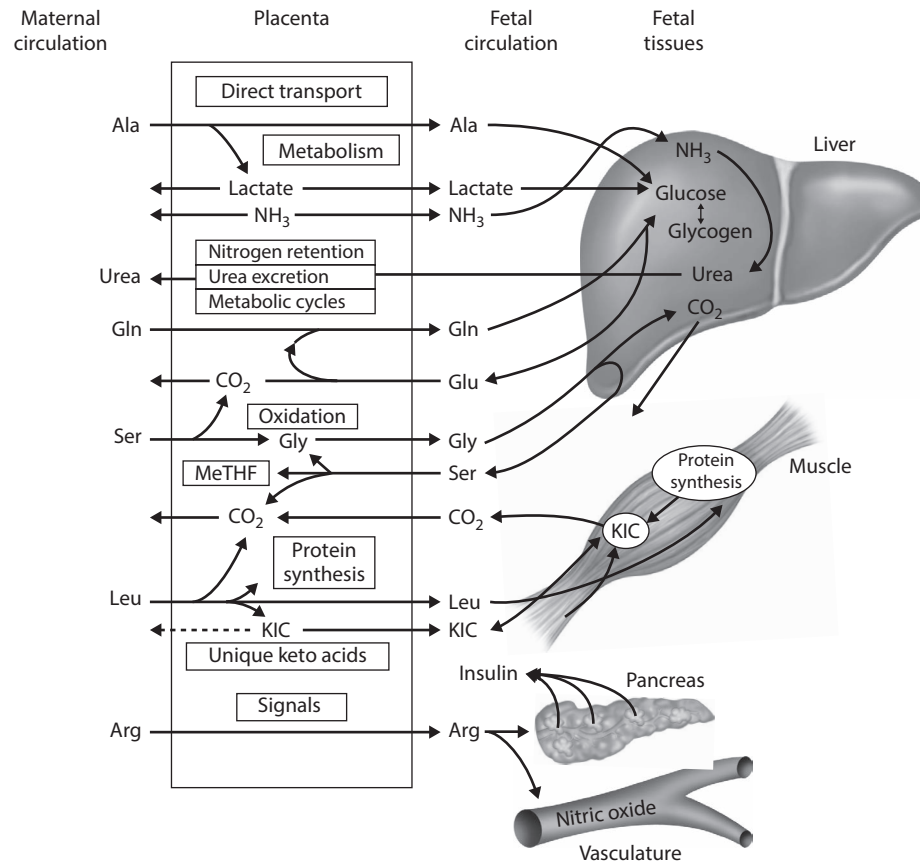


Figure 5.5 Schematic representation of a variety of placental–fetal metabolic interactions with respect to amino acid uptake by the placenta, metabolism in the trophoblast cells, direct transfer to the fetus, signaling of fetal vascular and metabolic processes, and utilization in fetal tissues. Ala, alanine; Gln, glutamine; Glu, glutamate; Ser, serine; Gly, glycine; Leu, leucine; KIC, α -ketoisocaproic acid; Arg, arginine; MeTHF, methyl-tetrahydrofolate; NH_3 , ammonia. (Adapted from Hay, W.W., Jr., *Placenta*, 16, 19, 1995; Reprinted from *Fetal and Neonatal Physiology*, 4th edn., Hay, W.W., Jr., Brown, L.D., and Regnault, T.R.H., Fetal requirements and placental transfer of nitrogenous compounds, pp. 585–602, Copyright 2011, with permission from Elsevier.)

This active transport process is decreased by hypoxia and inhibitors of protein synthesis,^{124,125} while hypoaminoacidemia increases transport, indicating that synthesis of the transporters is in part responsible for their functional state.¹²⁶ Net total fetal amino acid uptake can account for up to 30%–40% of the combined carbon requirements for oxidative metabolism and deposition in fetal protein, glycogen, and fat, providing 100% of the fetal nitrogen requirements.^{127,128} The placenta and fetus also interact in a variety of ways to ensure amino acid supply to a large and complex set of vital developmental, metabolic, and signaling processes that are unique to fetal growth and development (Figure 5.5).⁵

Fetal amino acid metabolism

Fetal amino acid oxidation

Evidence for a relatively high rate of fetal oxidation of amino acids comes from three observations: Amino acids are taken up by the fetus in excess of their rate of deposition in fetal protein⁵; fetal urea production rates are quite high¹²⁹; and fetal infusions of carbon-labeled amino acids have produced fetal production and excretion of labeled carbon dioxide.⁶² The urea production rate in fetal sheep

can account for *c.* 0.46 g/day/kg of nitrogen excretion, which is *c.* 25% of fetal nitrogen uptake in amino acids. Such fetal urea production rates are large, exceeding neonatal and adult weight-specific rates, indicating relatively rapid protein turnover and oxidation in the fetus. Direct measurement of fetal amino acid oxidation using carbon-labeled isotopic tracers has determined fetal oxidation rates for leucine (*c.* 25% of utilization), lysine (*c.* 10% of utilization), and glycine (*c.* 13% of utilization).¹³⁰ These studies also demonstrated that the fetal oxidation/disposal rate ratio is directly related to the excess umbilical uptake of these amino acids above that required for protein accretion and to their plasma concentrations.^{127,131} Similarly, when amino acids are exogenously infused into fetal lambs during late gestation, the rates of leucine oxidation increase and the glucose/oxygen metabolic quotient decreases, indicating that the fetus will increase amino acid oxidation rates in lieu of glucose depending on substrate availability.¹³

Fetal protein synthesis and turnover

The net umbilical uptake rates of several nonessential amino acids are less than their total rate of utilization, emphasizing the need for a relatively high rate of fetal amino acid

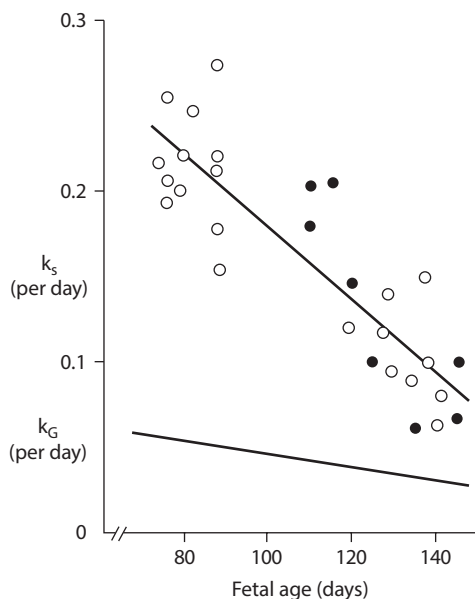


Figure 5.6 Fractional rate of protein synthesis (k_s) over gestation in fetal sheep studied with leucine (●) and lysine (○) radioactive tracers compared with the fractional rate of growth (k_G) in the lower portion of the figure. (Reprinted from *An Introduction to Fetal Physiology*, Battaglia, F.C. and Meschia, G., Copyright 1986, with permission from Elsevier; Meier, P.R. et al., *Am. J. Physiol.*, 240, E320, 1981; Kennaugh, J.M. et al., *Pediatr. Res.*, 22, 688, 1987.)

production.^{5,130} Protein synthetic rates also are high compared to the adult. Fractional protein synthetic rate (k_s) and fractional growth rate (k_G) are higher in the midgestation fetus compared to the near-term fetus, both proportional

to the higher metabolic rate and GUR at that stage of gestation.^{131,132} Thus, protein synthesis per millimole of oxygen consumed is quite constant from midgestation until term (Figure 5.6).

Skeletal muscle in the fetal sheep is a major consumer of both essential and nonessential amino acids from the circulation,¹³³ reflecting the relatively high rate of protein synthesis and nitrogen accretion of the fetus. Insulin and IGF-1 both have been shown to increase blood flow to the fetal hindlimb (used as an estimate of skeletal muscle-specific metabolic rates),^{133,134} promoting uptake of amino acids by the hindlimb. Euglycemic hyperinsulinemia also has been shown to promote the net uptake of several amino acids as well as increase glucose utilization by the fetal hindlimb.^{134,135} Therefore, it is reasonable to hypothesize that insulin-induced glucose utilization by muscle increases net protein balance, in part by substituting carbon from glucose for that of amino acids in the tricarboxylic acid cycle.¹³⁶

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6 Pathogenesis of gestational diabetes mellitus

Yariv Yogev

Introduction

Gestational diabetes mellitus (GDM) is characterized by carbohydrate intolerance of variable severity, with onset or first recognition during pregnancy. This definition applies whether or not there is a need for insulin and whether or not it disappears after the pregnancy. It does not apply to gravid patients with previously diagnosed diabetes.¹ A detailed discussion of glucose regulation in pregnancy is beyond the scope of this chapter. However, two points are important for the discussion that follows. First, pregnancy is normally attended by progressive insulin resistance that begins near midpregnancy and progresses through the third trimester to levels that approximate the insulin resistance seen in individuals with type 2 diabetes. The insulin resistance appears to result from a combination of increased maternal adiposity and the insulin-desensitizing effects of hormonal products of the placenta. The fact that insulin resistance rapidly abates following delivery suggests that the major contributors to this state of resistance are placental hormones. Second, pancreatic β cells normally increase their insulin secretion to compensate for the insulin resistance of pregnancy. As a result, changes in circulating glucose levels over the course of pregnancy are quite small compared with the large changes in insulin sensitivity. Robust plasticity of β -cell function in the face of progressive insulin resistance is the hallmark of normal glucose regulation during pregnancy.

Although pregnancy is a carbohydrate-intolerant state, only a small proportion of pregnant women (3%–5%) develop GDM. As pregnancy advances, the increasing tissue resistance to insulin creates a demand for more insulin. In the great majority of women, insulin requirements are readily met, so the balance between insulin resistance and insulin supply is maintained. However, if resistance becomes dominant due to impaired insulin secretion, hyperglycemia develops. In the majority of such cases, it develops in the last half of pregnancy, with insulin resistance increasing progressively until delivery, when, in most cases, it rapidly disappears.

Controversy still exists about the screening and diagnosis of GDM. In the majority of cases, carbohydrate intolerance is asymptomatic and can be detected only by routine

screening challenge tests. A detailed discussion of variations in the diagnostic criteria is beyond the scope of this chapter, but the main issue is that the diagnosis of GDM is based on the screening of a large number of apparently healthy young women.

As in type 1 diabetes mellitus, GDM is associated with both insulin resistance and impaired insulin secretion.^{2–4} The two disorders also share the same risk factors, have a corresponding prevalence within a given population, and have the same genetic susceptibility; therefore, they are assumed to be etiologically indistinct, with one preceding the other.

In this chapter, the development of insulin resistance during pregnancy, hormones, and newly discovered factors associated with insulin resistance and secretion, the insulin-signaling system during normal and diabetic pregnancy, and metabolic predictors of diabetes will be discussed.

Insulin sensitivity and resistance in pregnancy

The majority of women with GDM appear to have β -cell dysfunction that occurs on a background of chronic insulin resistance. As noted earlier, pregnancy normally induces quite marked insulin resistance. This physiological insulin resistance also occurs in women with GDM. However, it occurs on a background of chronic insulin resistance to which the insulin resistance of pregnancy is partially additive. As a result, pregnant women with GDM tend to have even greater insulin resistance than normal pregnant women.

The cellular mechanisms underlying insulin resistance in normal and diabetic pregnancy are still unknown. The measurement of fasting insulin concentrations and the calculation of fasting insulin/glucose ratios can provide a qualitative but not a quantitative estimation of insulin sensitivity. In nonpregnant patients, hyperinsulinemic–euglycemic clamps⁵ and minimal model analysis of intravenous glucose tolerance tests (IVGTTs)^{6,7} have been used to obtain quantitative data about insulin action. The IVGTT model provides data on the glucose infusion that is required to maintain euglycemia during constant insulin infusion. However, its use in pregnancy

is limited owing to the change in the relationship between common measures of body size, such as total body weight and body surface area. Catalano et al.^{8,9} were the first to conduct a prospective longitudinal study using the hyperinsulinemic–euglycemic clamp model in obese and nonobese gravid women with normal glucose tolerance tests. They found a 47% decrease in insulin sensitivity in obese gravid women and a 56% decrease in lean gravid women. Differences in whole-body insulin sensitivity tend to be small in the third trimester, owing to the marked effects of pregnancy itself on insulin resistance. Nonetheless, precise and direct measures of insulin sensitivity applied during the third trimester have identified, in women with GDM, exaggerated resistance to insulin's ability to stimulate glucose utilization.⁹

The development of resistance to the glucose-lowering effects of insulin is a normal phenomenon of pregnancy. In a pioneer study, Burt et al.¹⁰ demonstrated that pregnant women experience fewer hypoglycemic events in response to insulin infusion than nonpregnant women. Accordingly, later research found women with normal pregnancies had progressively exaggerated insulin responses to ingested glucose, together with a slightly decreased glucose tolerance.^{11,12} Using the IVGTT model, Buchanan et al.¹³ and Cousins et al.¹⁴ demonstrated a significant (70%) reduction in insulin sensitivity during the second trimester of normal pregnancy, with a return to normal values shortly after delivery. Ryan et al.² were the first to report quantitative differences in insulin sensitivity between normal and diabetic pregnancies. Other researchers noted that insulin sensitivity was lower in patients with GDM than in patients with normal pregnancies at 12–14 weeks of gestation, before the point of maximal physiological insulin resistance; however, the difference was not statistically significant. By the third trimester, insulin resistance was similar in the two groups.^{8,14}

Much effort has been invested to identify the tissues that contribute to the insulin resistance of pregnancy. Findings, in animal models, indicate a 40% reduction in insulin-mediated glucose utilization by skeletal muscle and a similar effect in cardiac muscle and fat cells.^{15,16}

It remains unclear whether hepatic insulin sensitivity is altered during gestation. Kalhan et al.¹⁷ and Cowett et al.¹⁸ noted no significant differences in basal glucose production in pregnant women at term compared to nonpregnant control subjects when the data were expressed per kilogram of body weight; however, expression of the data in relation to pregravid weight yielded an increase in hepatic glucose production in late pregnancy.¹⁹ Furthermore, in hyperinsulinemic–euglycemic clamp studies, hepatic glucose production was significantly less suppressed in lean and obese patients with GDM than in the control group.^{8,9}

Hormonal effect in normal and diabetic pregnancy

Reproductive hormones tend to increase during pregnancy, most of them contribute to insulin resistance and altered beta-cell function.

Estrogen and progesterone

In early pregnancy, both progesterone and estrogen rise but their effects on insulin activity are counterbalanced. Progesterone causes insulin resistance, whereas estrogen is protective.²⁰ An IVGTT given to estrogen-treated rats showed a significant decrease in glucose concentrations and a twofold increase in insulin concentration²¹; the addition of progesterone was associated with a 70% increase in the insulin response to a glucose challenge test, but there were no alterations in glucose tolerance.²² In cultured rat adipocyte tissue treated with estrogen, there was no effect on glucose transport, but maximum insulin binding was increased. However, progesterone decreased both maximum glucose transport and insulin binding.^{20,21}

Gonzalez et al.²³ evaluated the role played by progesterone and/or 17beta-estradiol on sensitivity to insulin action that took place during pregnancy. Ovariectomized rats were treated with different doses of progesterone and/or 17beta-estradiol in order to simulate the plasma levels in normal pregnancy rats. A hyperinsulinemic–euglycemic clamp was used to measure insulin sensitivity. The results suggested that the absence of female steroid hormones leads to decreased insulin sensitivity. Thus, the rise in insulin sensitivity during early pregnancy, when plasma concentrations of 17beta-estradiol and progesterone are low, could be due to 17beta-estradiol. However, during late pregnancy, when both plasma concentrations of 17beta-estradiol and progesterone are high, the role of 17beta-estradiol may serve to antagonize the effect of progesterone, diminishing insulin sensitivity.²³

Cortisol

Cortisol levels increase as pregnancy advances and by the end of pregnancy concentrations are threefold higher than in the nonpregnant state.²⁴ Rizza et al.,²⁵ in a clamp study, demonstrated that under infusion of high amounts of cortisol, hepatic glucose production increased and insulin sensitivity decreased. Findings in a skeletal muscle model showed that an excess of glucocorticoid is characterized by decreased total tyrosine phosphorylation of the insulin receptor (IR); therefore, it seems logical that glucocorticoid-induced insulin resistance is related to a postreceptor mechanism. In a study by Ahmed and Shalaye,²⁶ 30 pregnant women with GDM and 30 pregnant women with impaired glucose tolerance (IGT) were compared with 30 pregnant women with normal glucose tolerance. The GDM and IGT groups were found to have significantly higher levels of serum cortisol than the control group.

Prolactin

During pregnancy, maternal prolactin levels increase 7–10-fold. Gustafson et al.²⁷ reported that the basal insulin concentration and postchallenge glucose and insulin responses were greater in women with hyperprolactinemia than in healthy controls. These findings were supported by studies showing that the culture of pancreatic islet cells with prolactin induces an increase in insulin secretion.²⁸ Skouby et al.²⁹

investigated the relationship between the deterioration in glucose tolerance and plasma prolactin levels in patients with normal and diabetic pregnancies. Oral glucose tolerance tests (OGTTs) were performed in late pregnancy and postpartum. In late pregnancy, the GDM group had significantly elevated fasting glucose levels compared to the controls, and, after glucose challenge, their insulin responses were significantly diminished and the suppression of glucagon less pronounced. These differences in glucose metabolism were markedly reduced in the early postpartum period. There was no difference in basal prolactin concentrations between the two groups at either time point. The prolactin levels were also not altered during the OGTTs, and there was no correlation between the deterioration in glucose tolerance and the prolactin concentrations in either group. Thus, abnormal prolactin levels are not of pathophysiologic importance in the development of GDM.

Human placental lactogen

Human placental lactogen (hPL) levels rise at the beginning of the second trimester, causing a decrease in phosphorylation of insulin receptor substrate (IRS)-1 and profound insulin resistance.²⁰ Beck and Daughday³⁰ demonstrated that overnight infusion of hPL results in abnormal glucose tolerance and increased insulin and glucose concentration in response to an oral glucose challenge. Accordingly, Brelje et al.³¹ found that in islet cell culture, hPL directly stimulates insulin secretion. This may indicate that hPL directly regulates islet cell function and is probably the principal hormone responsible for the increase in islet function observed during normal pregnancy.³¹

Leptin

Leptin is a 16 kDa protein encoded by the *ob/ob* (obesity) gene secreted by adipocyte tissue. It can modulate energy expenditure by direct action on the hypothalamus. Fasting insulin and leptin concentrations correlate closely with body fat, making leptin a good marker of obesity and insulin resistance. As receptors to leptin are found in skeletal muscle, the liver, the pancreas, adipocyte tissue, the uterus, and the placenta, it may be responsible for both peripheral and central insulin resistance. Reductions in leptin concentrations are caused by weight loss, fasting, and starvation; leptin concentrations are increased with weight gain and hyperinsulinemia.

In animal models, using hyperinsulinemic-euglycemic clamp studies, infusion of leptin was found to increase the glucose infusion rate.³² Leptin levels are significantly higher in pregnancy than in the nonpregnant state, especially during the second and third trimesters,^{33–35} and this change in circulating leptin concentrations is generally consistent with changes in maternal fat stores and glucose metabolism. Results of studies by Laivuori et al.³⁶ suggest that pregnancy-associated increases in maternal plasma leptin may result from an upregulation of adipocyte leptin synthesis in the presence of increasing insulin resistance and hyperinsulinemia in the latter half of pregnancy. Investigators have also

shown that leptin directly affects whole body insulin sensitivity by regulating the efficiency of insulin-mediated glucose metabolism by skeletal muscle³⁷ and by hepatic regulation of gluconeogenesis.³⁸ Leptin may also wield an acute inhibitory effect on insulin secretion.³⁹ Yamashita et al.⁴⁰ suggested that an alteration in leptin action might play a role in GDM and fetal overgrowth weight gain. They found that pregnant mice treated with leptin had markedly lower glucose levels than controls during glucose and insulin challenge tests. However, despite the reduced energy intake and improved glucose tolerance, fetal overgrowth was not reduced. Results provide evidence that leptin administration during late gestation can reduce adiposity and improve glucose tolerance in the model of spontaneous GDM. These data suggest that alterations in placental leptin levels may contribute to the regulation of fetal growth independently of maternal glucose levels.

Kautzky-Willer et al.⁴¹ measured plasma concentrations of leptin and beta-cell hormones during fasting and after an oral glucose load (OGTT of 75 g) in pregnant women with GDM and normal glucose tolerance at 28 weeks gestation and in women who were not pregnant. Plasma leptin concentration was higher in the women with GDM than in the women with normal glucose tolerance and higher in both these groups than in the nonpregnant controls. No change in plasma leptin concentrations was induced by OGTT in any group. Basal insulin release was higher in women with GDM than in women with normal glucose tolerance. The authors concluded that women with GDM and no change in plasma leptin on oral glucose loading have increased plasma leptin concentrations during and after pregnancy. Vitoratos et al.⁴² investigated the changes in leptin levels and the relationship between leptin substance and insulin and glucose in pregnant women with GDM. Plasma leptin levels were measured in peripheral vein blood samples from healthy and diabetic women at 29 and 33 weeks gestation. Results showed a correlation of plasma leptin levels with fasting plasma insulin levels and plasma glucose levels measured 1 hour after oral administration of 50 g of glucose. Serum leptin levels were significantly higher in the women with GDM than in the women with uncomplicated pregnancies. The GDM group also showed a significant, positive correlation of serum leptin levels with glycosylated hemoglobin levels, fasting serum insulin levels, and plasma glucose levels measured 1 hour after administration of 50 g of glucose. Thus, levels of leptin are elevated in women with GDM, and leptin metabolism depends on insulin levels and the severity of the diabetes. Wiznitzer et al.⁴³ reported that umbilical cord leptin concentration was an independent risk factor for fetal macrosomia in nondiabetic pregnant women.

Other factors affecting gestational diabetes mellitus

Tumor necrosis factor-alpha

Tumor necrosis factor-alpha (TNF- α) has been implicated in the pathogenesis of insulin resistance in type 2 diabetes mellitus, but only limited data are available with regard to GDM.

Coughlan et al.⁴⁴ investigated the effect of exogenous glucose on the release of TNF- α from placental and adipose tissue obtained from normal and diabetic pregnant women. They found significantly greater TNF- α release under conditions of high glucose concentrations in the GDM group. As TNF- α has been implicated in the regulation of glucose and lipid metabolism, and in insulin resistance, these data are consistent with the hypothesis that TNF- α is involved in the pathogenesis and/or progression of GDM.

Catalano et al.⁴⁵ reported that changes in insulin sensitivity from early to late pregnancy correlated with a gradual increase in TNF- α levels, which in turn correlated with the percentage change in body weight.

Adrenomedullin

Adrenomedullin is a newly discovered hypotensive peptide involved in the insulin regulatory system, and it may play a role in modifying diabetes in pregnancy. Di Iorio et al.⁴⁶ studied its correlation to GDM. Adrenomedullin concentrations were measured in maternal and fetal plasma and in amniotic fluid in diabetic and nondiabetic pregnancies. Overall amniotic fluid concentration was higher in the pregnant diabetic women (type 1 or GDM), but there was no difference between the group in maternal and fetal plasma levels. These findings suggest that placental adrenomedullin production is upregulated in diabetic pregnancy and that it may be important to prevent excessive vasoconstriction of placental vessels.

Adiponectin

Adiponectin is an adipose tissue hormone, which is a specific plasma protein that is secreted by adipocytes. It may facilitate the regulation of the glucose and lipid metabolism. Adiponectin decreases the hepatic glucose production and insulin resistance by upregulating fatty acid oxidation.⁴⁷ Adiponectin also suppresses the secretion of TNF- α by adipose tissue, a factor that is known to contribute to insulin resistance.⁴⁸ Studies have shown that adiponectin serum levels were decreased in obese subjects⁴⁹ and patients with type 2 diabetes.⁵⁰ In studies with rhesus monkeys, adiponectin plasma levels were significantly decreased with the progression of obesity and insulin resistance.⁵¹ In all probability, adiponectin increases insulin sensitivity by enhancing the β -oxidation of free fatty acids and by decreasing the intracellular concentrations of triglycerides.^{52,53} In patients with type 2 diabetes, who have the same risk factors for GDM, i.e., obesity, maternal age, ethnic origin, and family history, lower serum levels of adiponectin were detected. In mice, the intravenous administration of adiponectin was associated with loss of weight and reduced plasma concentrations of fatty acids⁵⁴; the proportion of total body fat mass was correlated negatively with adiponectin serum levels.⁵⁵ The data suggests that low plasma adiponectin concentration during even early pregnancy may be associated with subsequent development of GDM.^{56–58} Levels of adiponectin have been assessed in fetal cord at delivery.⁵⁸ A cord blood adiponectin

level was extremely high in comparison to serum levels in children and adults and was positively correlated to fetal birth weights. No correlation was found between cord adiponectin levels and maternal body mass index, cord leptin, or insulin levels. Cord adiponectin levels were significantly higher compared with maternal levels at birth, and no correlation was found between cord and maternal adiponectin levels. There were no significant differences between adiponectin levels at birth and 4 days postpartum. These findings indicate that adiponectin in cord blood is derived from fetal and not from placental or maternal tissues. The high adiponectin levels in newborns compared with adults may be the result of deficient negative feedback on adiponectin production stemming from the lack of adipocyte hypertrophy, low percentage of body fat, or a different distribution of fat storage in newborns. Adiponectin may emerge as a significant factor in carbohydrate–fat metabolism and in the development of insulin resistance during pregnancy. Data suggest that there are decreased adiponectin levels in women with GDM compared with healthy control subjects. This finding supports the concept of a common pathogenesis between type 2 diabetes and GDM. Although adiponectin level appears to rise throughout pregnancy, its contribution to gestation remains unclear.

Pancreatic beta-cell function in normal pregnancy and gestational diabetes mellitus

Insulin is the main hormone controlling blood glucose concentration. Most commonly, assessment of beta-cell function is made by measuring the fasting insulin concentration or the response to glucose infusion. Fasting plasma insulin increases gradually during pregnancy—by the third trimester, levels are twofold higher than before pregnancy. Patients with GDM have fasting insulin levels equal to or higher than those of women with nondiabetic pregnancies, with the highest levels occurring in obese women with GDM.

During normal pregnancy, oral and intravenous glucose tolerance deteriorates only slightly, despite the reduction in insulin sensitivity.¹³ The main mechanism responsible for that phenomenon is a gradual increase in insulin secretion by the beta cells. Kuhl¹² reported a hyperbolic relationship between insulin sensitivity and beta-cell responsiveness to glucose in both pregnant and nonpregnant women, pointing to a role for the beta cells in pathological states such as GDM and demonstrating the magnitude of the change in insulin secretion that is necessary to maintain glucose tolerance. The mechanism responsible for increase insulin secretion during pregnancy is not well understood. A major contributing factor is the increase in the beta-cell mass, a combination of hyperplasia and hypertrophy.⁵⁹ The increased beta-cell mass can contribute to the increased fasting insulin concentration despite normal or lowered fasting glucose concentrations in late pregnancy, and the enhanced insulin response to glucose during pregnancy (twofold to threefold above nonpregnant levels).

In GDM, the early insulin response to OGTT (15–30 minutes after glucose ingestion) is reduced compared to nondiabetic pregnant control women, suggesting a defect in the beta-cell response.⁶⁰ First-phase beta-cell responses to glucose infusion in GDM patients has also been reported to be reduced. GDM tends to be milder in women with a normal beta-cell response, and they are at relatively low risk for developing diabetes.⁶¹

Genetics, immunology, and gestational diabetes mellitus

Some patients with GDM manifest evidence for autoimmunity toward beta cells (insulin autoantibodies and anti-islet cell antibodies); however, the prevalence of such autoimmunity has been reported to be extremely low (<10%).^{62,63} Mutations in the glucokinase gene occur in no more than 5% of patients with GDM.⁶⁴ The inheritance of GDM was studied in a group of 100 women with previous GDM.⁶⁵ The women were reinvestigated 11 years postpartum and 60% were found to have either IGT or type 2 diabetes. An investigation of their parents showed that a substantial proportion had neither parent affected with IGT or type 2 diabetes, which suggests a polygenic inheritance or environmental influence rather than autosomal dominance inheritance with high penetration rates. In addition, animal studies have shown that prenatal exposure to a diabetic intrauterine milieu increases the risk of GDM.

Harder et al.⁶⁶ reported that the prevalence of type 2 diabetes was significantly greater in mothers than in fathers of women with GDM, and there was also significant aggregation of type 2 diabetes in the maternal–grandmaternal line compared to the paternal–grandpaternal line. Therefore, that may suggest that a history of type 2 diabetes on the mother's side might be considered as a particular risk factor for GDM.

The possible genetic background of GDM remains unclear. In particular, its association with human leukocyte antigen (HLA) class II polymorphism has been poorly studied, and the results are conflicting. In an attempt to clarify these discrepancies, Vambergue et al.⁶⁷ reported that the distribution of HLA class II polymorphism was not significantly different between GDM and IGT samples, and there was no significant variation in DRB1*03 and DRB1*04 allele frequencies. These data provide further evidence that type 1 or insulin-dependent diabetes mellitus HLA class II susceptibility alleles cannot serve as genetic markers for susceptibility to glucose intolerance during pregnancy.

Ober et al.⁶⁸ studied the restriction fragment length polymorphisms near “candidate diabetogenic genes” in order to identify molecular markers for GDM genes. Genotypes for the insulin hypervariable region, insulin-like growth factor 2 (IGF2), IR, and glucose transporter (GLUT)1 were studied in GDM and control subjects. The results supported the hypotheses that GDM has heterogeneous phenotypic and genotypic features and that the risk for GDM in black and Caucasian subjects is not related to obesity per se but to interactions between obesity and IR alleles. In Caucasian women, IR and IGF2 alleles interact to confer an additional risk for GDM. Thus, in some women, genes responsible for susceptibility to

GDM may be similar to the genes conferring risk of type 2 diabetes, whereas in others, novel genes may contribute to GDM.

Insulin signaling system in normal pregnancy and in gestational diabetes mellitus

The action of insulin is triggered when it binds to the IR. The IR belongs to the IGF receptor family, which possesses an intrinsic tyrosine kinase (TK) activity. The receptor is composed of two alpha-subunits, each linked to a beta-subunit and to each other by disulfide bonds; only the beta-subunit has enzymatic TK activity. When insulin binds to the receptor, the conformational change activates the beta-subunit and autophosphorylation begins. Thus, the activation of TK enzyme leads to increased tyrosine phosphorylation of cellular substrates. IRS-1, a cytosolic protein, binds to the phosphorylated intracellular substrates, thereby transmitting the insulin signal downstream. The distribution of the IRS proteins tends to be tissue specific: IRS-2 is more copious in the liver and pancreas, whereas both IRS-1 and IRS-2 are widely expressed in skeletal muscle. Insulin stimulates the activation and binding of the lipid kinase enzyme, phosphatidylinositol (PI)-3-kinase, and its binding to IRS-1. The formation of PI is mandatory for insulin action on glucose transport. Knockout of the IRS-1 gene causes only a moderate increase in insulin resistance due to increased insulin secretion, but not overt diabetes. In women with GDM, the skeletal muscle contains lower levels of IRS-1 protein and significantly less insulin-stimulated IRS-1 tyrosine phosphorylation, while levels of the IRS-2 protein are increased. These findings suggest that the insulin resistance of GDM may be exerted through a decrease in the insulin resistance cascade at the level of the IRS proteins. The increased IRS-2 level may be a compensation for the reduced IRS-1 level.⁶⁹ Glucose uptake by cells is mediated by a family of membrane proteins, GLUT1–GLUT4, which have a significant sequence similarity. GLUT4 is the main insulin-sensitive glucose transport, expressed uniquely in skeletal and cardiac muscles and adipose tissue. Garvey et al.⁷⁰ reported that in rectus abdominis taken from lean and obese women with GDM, GLUT4 content was similar. In GDM, GLUT4 gene expression is normal in skeletal muscles. To the extent that these muscles are representative of the total muscle mass, insulin resistance in skeletal muscle may involve impaired GLUT4 function or translocation, but not its depletion, as observed in adipose tissue. Garvey et al.⁷¹ demonstrated that the insulin-stimulated glucose transport in adipocyte tissue was reduced by 60% at term in women with GDM compared to nondiabetic pregnant women. Moreover, the GLUT4 content in adipocytes was profoundly depleted in 50% of the GDM group. The whole group exhibited a novel abnormality in GLUT4 subcellular distribution, an accumulation of GLUT4 in membranes cofractionating with plasma membranes and high-density microsomes in basal cells, and absence of translocation in response to insulin. These data suggest that abnormalities in cellular traffic or targeting relegate GLUT4 to a membrane compartment from which insulin cannot recruit transporters to the cell surface. This has important implications for skeletal muscle insulin resistance in GDM.

The membrane protein plasma cell membrane glycoprotein-1 (PC-1) has been identified as an inhibitor of insulin receptor TK (IRTK) activity. Shao et al.⁶⁹ investigated IR function and PC-1 levels in the muscle from three groups of obese subjects: women with GDM, pregnant women with normal glucose tolerance, and nonpregnant control subjects. No significant differences were found in basal IR tyrosine phosphorylation or IRTK activity among the three groups. After maximal insulin stimulation, IRTK activity increased in all subjects, but was lower in women with GDM by 25% and 39% compared with pregnant and nonpregnant control subjects, respectively. Similarly, IR tyrosine phosphorylation was significantly decreased in the subjects with GDM compared to the other two groups. Treatment of the IR with alkaline phosphatase to dephosphorylate serine/threonine residues significantly increased insulin-stimulated IRTK activity in the pregnant control and GDM subjects, but the rates were still lower than in the nonpregnant controls. PC-1 content in the muscle from GDM subjects was increased by 63% compared with pregnant control subjects and by 206% compared with nonpregnant control subjects. PC-1 content was negatively correlated with IR phosphorylation and IRTK. Increased PC-1 content in the pregnant control and GDM groups suggests an excessive phosphorylation of serine/threonine residues in muscle IR, both of which may contribute to the pregnancy-associated decrease in IRTK activity. In GDM, changes worsened, even when controlling for obesity. These postreceptor defects in insulin signaling may contribute to the pathogenesis of GDM and the increased risk for type 2 diabetes later in life.

Receptor autophosphorylation has also been reported to be impaired in GDM subjects, a finding consistent with their increased insulin resistance.⁷⁰ In addition, overexpression of membrane plasma cell differentiation factor-1 (i.e., PC-1) may play a role in developing insulin resistance by inhibiting the TK activity of the IR.⁷¹ In GDM patients, PC-1 levels were significantly higher in skeletal muscle compared to nondiabetic pregnant women.⁷²

Summary

GDM is carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy. The incidence of GDM is 0.15%–15%,

and it corresponds to the prevalence of type 2 diabetes and IGT within a given population. The predominant pathogenic factor in GDM could be inadequate insulin secretion. It has been convincingly demonstrated that GDM occurs as a result of a combination of insulin resistance and decreased insulin secretion. The similar frequencies of HLA-DR2, HLA-DR3, and HLA-DR4 antigens in healthy pregnant women and women with GDM, and the low prevalence of markers for autoimmune destruction of the beta cells in GDM, rule out the possibility that GDM has an autoimmune origin. Pregnancy is associated with profound hormonal changes that have a direct effect on carbohydrate tolerance. In early pregnancy, both progesterone and estrogen levels rise, but their actions on insulin are counterbalanced, as progesterone causes insulin resistance and estrogen is protective. In the second trimester, hPL, cortisol, and prolactin levels all rise, causing decreased phosphorylation of IRS-1 and profound insulin resistance. In most subjects, pancreatic insulin secretion rise to meet this need, but in those with underlying beta-cell defects, hyperglycemia ensues. In women with GDM, the insulin resistance of pregnancy is exaggerated, especially if fasting hyperglycemia is present, and is related to additional defective tyrosine phosphorylation of the IR beta-subunit. Recent research suggests that the postreceptor mechanisms that contribute to insulin resistance of pregnancy are multifactorial but are exerted at the beta-subunit of the IR and at the level of IRS-1. The resistance to insulin-mediated glucose transport appears to be greater in the skeletal muscle from GDM subjects than from pregnant subjects. There is also a modest but significant decrease in the maximal IR tyrosine phosphorylation in the muscle from obese GDM subjects. Results also suggest that increased IR serine/threonine phosphorylation and PC-1 could underlie the insulin resistance of pregnancy and contribute to the pathogenesis of GDM.

Whether additional defects are exerted further downstream from IRS-1 remains to be investigated. GDM is a predictor of diabetes (mainly type 2) later in life. The cumulative incidence of type 2 diabetes is 50% at 5 years. GDM is also a predictor, or even an early manifestation, of the metabolic (insulin resistance) syndrome. GDM is a cardiovascular risk factor, and affected patients should be screened to prevent late complications.

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7 Autoimmunity in gestational diabetes mellitus

Alberto de Leiva, Dídac Mauricio, and Rosa Corcoy

Immunobiology of GDM

Pregnancy represents a distinct immunologic state; the fetus acts as an allograft to the mother, needing protection against potential rejection.^{1,2} Humoral immunoreactivity does not change much during pregnancy, with the exception of lowered immunoglobulin G concentration at late phase, probably explained by placental transport.³ Regarding cellular immunity, reduction,^{4,5} elevation,⁶ and no variation⁷ in the number of different lymphocytic populations have been reported. The final effect of pregnancy on previously active autoimmune processes is controversial,^{8,9} and multiple autoimmune disturbances may be manifested during pregnancy.¹⁰

In diabetic pregnancy, immunological abnormalities occurring in diabetes are superimposed on immunological changes of pregnancy, eventually influencing maternal and fetal outcomes. The interplay between sex hormones and the immune system is complex and multifactorial, affecting many organs and systems. The mechanisms of estrogen and progesterone modulation of individual components of the immune system have been extensively studied *in vitro* but not in humans. Older concepts of pregnancy as a state of systemic immunosuppression are oversimplified. A more useful model may be the view of pregnancy as a modulated immunologic condition. As pregnancy advances, T-cell activity, natural killer activity, and possibly B-cell activity are reduced, whereas α -defensin levels and monocytic, dendritic cell and polymorphonuclear cell activities are increased. In general, levels of inflammatory cytokines are reduced, whereas levels of cytokines that induce phagocytic-cell recruitment or activity are increased; these alterations do not necessarily follow a clear Th1 or Th2 phenotype.

Gestational diabetes mellitus (GDM) is defined as an impairment of glucose tolerance first recognized at the index pregnancy.¹¹ For this category of women, an increased risk of progression to type 2 diabetes mellitus (DM-2) has been repeatedly reported.^{12–15} Nevertheless, a subset of women with GDM depicts one or several autoantibodies (AA) against various pancreatic islet cell autoantigens, typically detected in type 1 diabetes mellitus (DM-1)¹⁶ as well as in high-risk subjects for the development of the disease, in particular,

first-degree relatives of patients with DM-1 (FDRs-DM-1).¹⁷ In type 1A diabetes, a selective destruction of the insulin-producing cells occurred, mediated by T cells.

Diabetes-related antibodies and pregnancy

Prevalence and titers

Circulating islet cell antibodies, originally described by indirect immunofluorescence in 1974,¹⁸ have been demonstrated in the great majority of individuals with autoimmune diabetes, both at the preclinical state and at the onset of clinically overt diabetes, and they persist in the circulation for a long time. Most investigated islet cell AAs include AAs to islet cell cytoplasm (islet cell AAs [ICAs]), to native insulin (insulin AAs [IAAs]), to GAD (GADA),^{19–21} and to tyrosine phosphatases (insulinoma-associated antigens IA-2A and IA-2 β)^{22,23}:

ICAs. The prevalence of cytoplasmic islet cell antibodies in GDM has been reported to range between 0.98% and 14.7% in Caucasians,^{1–3,14–32} higher than in the control group,^{14,25,27,33–35} except in studies with low statistical power.^{36–38} Characteristically, ICA titers are low when compared with subjects with new-onset type 1A diabetes and their FDRs.^{28,33–39}

IAAs. The presence of IAAs in sera of subjects with DM-1 before initiating insulin treatment was first reported in 1982.⁴⁰ Since then, IAAs have been shown in 20%–50% of patients with DM-1 of recent diagnosis. IAA positivity displays a strong negative association with age: IAAs are positive in 90% of children who develop DM-1 before the age of 5 years, but in less than 40% after the age of 12 years.⁴¹ This result is in accordance with the low prevalence of IAAs in women with GDM (0%–5.9%), even when addressed just by a low number of studies,^{25,27,36–39} with only one of them reporting a higher prevalence than in the control population.²⁷ When positive, IAA titers are also lower than those of patients with DM-1 and their FDRs.³⁸ We have investigated the frequency of IAAs in women with GDM

using a radiobinding assay. We observed that only 0.98% (2 of 203) of consecutive women at diagnosis of GDM displayed IAAs in their sera before initiation of treatment (registered frequency in control subjects, 0 of 106 individuals; frequency in FDRs-DM-1, 4.7%). Interestingly, in the subgroup of ICA (+) women with GDM, the prevalence of IAAs was higher than in ICA (–) ones (11% vs. 0.7%), so that in women with GDM and ICA positivity, the prevalence of IAAs was not different than in FDRs-DM-1.²⁵ Quite a different issue is the appearance of insulin antibodies (IAs) in women with GDM treated with exogenous insulin. Our group has reported that 44% of women receiving human insulin therapy for GDM develop IAs, which may persist up to 24 months after delivery.⁴² Similar findings have been described after treatment with lispro-insulin.⁴³

GADAs and IA-2As. GAD is the biosynthesizing enzyme of γ -aminobutyric acid. Pancreatic β -cells express this enzyme, among other cell types. The prevalence of these AAs in subjects with new-onset DM-1 is 60%–70% for GADAs, 40% for IA-2As, and 20% for IA-2 β As.^{44,45} All DRAAs could be useful for the screening of autoimmune diabetes. Because ICA measurement is time consuming and semiquantitative, currently it is usually used for confirmation purposes. The combination of two antibodies offers a good yield with GADAs/IA-2As and GADAs/IAAs being used in adults and children, respectively.⁴⁶ Our group has reported that nonisotopic alternatives for GADA65 and IA-2As are suitable for the precise use of estimation of risk prediction and diagnosis of autoimmune diabetes.⁴⁷

Some reports have shown that the prevalence of IA-2As in GDM ranges from 0% to 6.2%.^{27,34,38,48,49} Several articles have compared the prevalence of IA-2As in women with GDM with that of a control population, the figures being higher in two articles^{25,34} and similar in the other two.^{27,38} These antibodies are not frequent in this age range⁵⁰ and are associated with rapid progression to severe insulinopenia.⁵¹ IA-2A titers in women with GDM are lower than in children with type 1A diabetes.⁴⁸ The prevalence of GADAs in GDM has been reported to range from 0% to 10.8%,^{25,27,34,35,38,48,49,52,53,59,60–63,99} with an article from India describing a prevalence of 41% for GADAs/IA-2As.⁵⁹ Several reasons may account for these heterogeneous findings. First, each population has a different genetic and environmental background that confer different risks. Second, in each population, different ethnic groups may have different susceptibility for GDM and to β -cell autoimmunity. Third, methodological issues, such as study design or laboratory procedures, may justify these wide differences. As in the case of ICAs, their frequency has been reported to be higher than in the control population in some^{25,27,34,35,62} but not all articles,^{38,54,55,58,63} probably because of the low statistical power of the latter. As for other diabetes-related antibodies (DRAs), titers of GADAs in GDM have also been reported to be lower when compared with type 1A diabetes, autoimmune prediabetes, and

FDRs-DM-1.^{35,60} Table 7.1 illustrates the prevalence of DRAs in GDM, reported in multiple publications.

A prospective German multicentric study has shown that GADAs in women with GDM bound fewer epitopes than GADAs in FDRs-DM-1.⁶⁰ Whereas the prevalence and titers of GADAs to the major GAD65 COOH-terminal middle epitope were not significantly different (91% vs. 100%, 88.6% vs. 100%), AAs to epitopes GAD65-midb (middle b) and GAD67 were less frequently detected in patients with GDM (57% vs. 90%, 38% vs. 79%). AAs reactive to all epitopes of GAD65 tested in this study were also less frequent in subjects with GDM, in comparison to FDRs-DM-1 (65% vs. 23%, $p < 0.01$). The observed reduction of binding to GAD epitopes in women with GDM, in comparison with young FDRs-DM-1, is also seen in latent autoimmune diabetes of adulthood (LADA) patients.⁶¹ Similar to LADA, in GDM, the combined presence of various AAs is infrequent,^{25,27,34,48,49} which is consistent with the concept of a slow progression form of autoimmune diabetes.⁶⁰

Transplacental passage of DRAs and related effects. DRAs are transferred to the fetus.^{42,62–67} They are mainly IgG and are actively transported by the placenta.^{68,69} Maternal and fetal levels are highly correlated for IAs,^{42,62,64–66} ICAs,⁴⁶ GADAs,^{62,70} and IA-2As.⁶² This transplacental passage of antibodies lies behind the higher prevalence of DRA in cord blood from infants of diabetic mothers compared with infants of diabetic fathers.⁶⁷ Postnatal elimination of transplacentally acquired DRAs has been prospectively investigated in infants born to type 1 diabetic mothers, with the mean elimination time being 3.1 months for ICAs and IAs, 4.5 months for GADAs, and 4.3 months for IA-2As.⁷²

Menon et al.⁶⁴ reported that the concentration of animal insulin in cord serum correlated with birth weight, but this observation has not been confirmed by other authors.^{42,65,66,71,72} The underlying mechanism would be an IA-facilitated maternal insulin transfer and, as a consequence, an enhancement of fetal hyperinsulinism and related morbidity.⁷³ Maternal insulin–IA complexes have been associated with toxemia,^{27,74,75} HELLP syndrome,⁷⁶ hypoglycemia,^{27,77} respiratory distress,²⁷ and high hematocrit in the newborn.⁷⁶ Nevertheless, other investigators have not observed a relationship between maternal levels of IAs and cord blood levels of insulin, 32–33 split proinsulin,⁷² or C-peptide.⁶⁵ In our experience, fetal outcomes were not influenced by the presence or titers of IAs, IAAs, or ICAs.⁷⁸

In the nonobese diabetic mouse, the transplacental passage of maternal AAs increases the risk of experimental autoimmune diabetes in the offspring,⁷⁹ whereas the transmission of AAs against activated T cells is protective.⁸⁰ Interestingly, in infants of diabetic mothers, the presence of GADAs and IA-2As, but not of IAs, in cord blood samples, is associated with a lower risk of developing DRAs and DM-1.⁸¹ However, when present in infants of diabetic fathers, DRAs are not protective, which seems to imply an active fetus self-immune response in this case.⁸¹

Table 7.1 Prevalence of diabetes-related antibodies in women with gestational diabetes mellitus (%)

Author	n	ICA	IAA	GADA	I-A2A
Steel et al. ²⁶	50	10			
Ginsberg-Fellner et al. ²⁹	88	35			
Fallucca et al. ²⁷	39	5			
Freinkel et al. ¹⁴	160	7.5			
Catalano et al. ³⁰	187	1.6			
Bell et al. ⁹⁶	181	2.8			
Stangenberg et al. ³¹	55	1.8			
Mauricio et al. ³³	307	12.4			
Ziegler et al. ³⁹	55	11			
Damm et al. ³⁶	139	2.9	0		
Tuomilehto et al. ⁵²	112			5.0	
Beischer et al. ⁵³	734			1.8	
Mauricio et al. ²⁵	203		1		
Petersen et al. ⁵⁴	139			2.2	
Dozio et al. ³⁸	145	10	3.0	0	0
Fuchtenbusch et al. ²⁸	437	8.5		9.5	6.2
Fallucca et al. ⁵⁵	83			3.6	
Whittingham et al. ⁴⁸	98	3		4	1
Panczel et al. ¹⁰⁹	68	14.7			
Kinalski et al. ³⁴	156	5.1		7.0	3.2
Mitchell et al. ⁵⁶	100			6	
Bartha et al. ⁹⁹	102	0.98		10.8	
Kousta et al. ⁵⁷	321			4.0	
Weng et al. ⁵⁸	66			4.5	
Balaji et al. ⁵⁹	86			41 GADA/IA-2	
Albareda et al. ⁴⁹	535	14		1.5	0.2
Bo et al. ³⁵	123	6.5		4.1	

Source: de Leiva, A. et al., *Diabetes Care*, 30(Suppl. 2), 127, 2007. With permission.

Heterogeneity of autoimmune diabetes

Autoimmune diabetes is caused by the destruction of β -cells of pancreatic islets by an immune-mediated process, promoted by the interaction of genetic and environmental factors.⁸² AAs against pancreatic β -cell antigens precede the clinical onset of DM-1.⁸² Patients with DM-1 have an increased risk of other autoimmune disorders, including Graves' disease, thyroiditis, Addison's disease, celiac disease, and pernicious anemia.

Age not only modifies the risk of autoimmune diabetes but also the presence of AAs, the intensity of beta-cell destruction, the rate of progression to overt diabetes, and the degree of residual insulin secretion. Approximately 30% of subjects with classic autoimmune diabetes (type 1A diabetes) present after age 35 years.⁸³ In Caucasians, childhood autoimmune diabetes is associated with an increased

prevalence of alleles DR3, DQB1*0201 and DR4, and DQB1*0302, with the proportion of heterozygotes declining with age at diagnosis.⁸⁴ Children with the allele HLA DR2, DQB1*0602, almost never develop diabetes, whereas this allele confers a much lower protection for adult-onset autoimmune diabetes.

A minority of patients with DM-1 have no known etiology and no evidence of autoimmunity (type 1B diabetes, idiopathic DM-1); most of these patients are of African or Asian origin. It is well known that autoimmunity against pancreatic islets may evolve in some instances as a highly aggressive process responsible of extreme insulinopenia, whereas in other occasions, it leads to a slow and nonaggressive process, practically asymptomatic, recognized by humoral autoimmunity markers.

During recent years, islet AAs have been demonstrated in the sera of a significant fraction (5%–20%) of individuals with phenotypical characteristics of DM-2. As a result,

the term LADA has been incorporated to define this new clinical variant of diabetes.^{85–87}

These patients with adult-onset autoimmune diabetes can be initially misclassified as having DM-2. Characteristically, they display a lower rate of metabolic syndrome than patients with DM-2.⁸⁸ The distinction between adult-onset DM-1 and LADA is sometimes difficult, but, characteristically, patients with LADA evolve slowly toward insulin requirement (within 6 years), and older patients with LADA show even a slower progression.^{86,89} The presence of GADA indicates a strong possibility of requiring insulin treatment earlier than expected in classical-type diabetes.

Some investigators believe that patterns of HLA susceptibility in LADA patients are similar to those reported for classic DM-1, supporting the hypothesis that the genetics of autoimmune diabetes in children and adults are differentiated by only relatively few age-dependent genetic effects and the slower progression of the insulin deficiency in adults may be related to subtle variation in the HLA class II gene associations.^{90,91} On the contrary, other researchers have proposed that LADA patients differ genetically from classical DM-1.^{92,93} Two distinct monocyte gene expression clusters have been identified in autoimmune diabetes. One cluster, comprising 12 pro-inflammatory cytokine/compound genes, was detected in 60% of LADA patients and 28% of adult-onset type 1 diabetic subjects but in only 10% of juvenile-onset type 1 diabetic patients. A second cluster, comprising 10 chemotaxis, adhesion, motility, and metabolism genes, was identified in 43% of juvenile autoimmune diabetes, 33% of LADA patients, and only 9% of adult-onset type 1 diabetic individuals.⁹²

Genetic markers in autoimmune GDM

Although genetic markers hold a most relevant promise for the future, they are of only limited clinical value in the evaluation and management of diabetic patients. To screen for the genetic susceptibility of type 1A diabetes, HLA typing is most useful. The HLA complex on chromosome 6p21.3 is a major susceptibility locus, *IDDM1*. The HLA complex contains class I and II genes that code for several polypeptide chains. The class I genes are HLA-A, HLA-B, and HLA-C. The loci of class II genes are designated by three letters: the first, -D-, indicates the class, the second (M, O, P, Q, R) the family, and the third (A or B) the chain. Both classes of molecules are heterodimers: class I exhibits an α -chain and β 2-microglobulin and class II exhibits α - and β -chains. The function of the HLA molecules is to present short peptides to T cells to initiate the immune response. Multiple genetic reports have demonstrated an association between various HLA alleles and autoimmune disorders.

In Caucasian patients with DM-1, HLA-D genes contribute as much as 50% of the genetic susceptibility.⁹⁴ HLA-DQ genes appear critical to the HLA-associated risk of DM-1A. In any individual, four possible DQ dimers are encoded; positive risks for the disease are associated with

α -chains that have an arginine residue 52 and β -chains that lack an aspartic acid at residue 57. The highest genetic risk corresponds to those persons in whom all four HLA-DQ combinations meet this criterion (heterozygous for *HLA DRB1*04-DQA1*0301-DQB1*0302* and *DRB1*03-DQA1*0501-DQB1*0201*), with an absolute lifetime risk for DM 1A in the general population of 1:12. On the contrary, persons who are protected are those with *DRB1*15-DQA1*0201-DQB1*0602* (*Asp57+*) haplotypes.⁹⁵ People carrying out the *B1*0401* and *0405* subtypes of *DRB1*04* are susceptible, whereas the **0403* and **0406* subtypes are protective.

So far, the genes of HLA complex have been the most investigated genetic factors in autoimmune GDM (AIGDM). The information obtained from various reports showed discordant results.^{14,36,37,96–98} In these protocols, the number of investigated subjects was small, and the analyzed populations quite heterogeneous. Rubinstein et al. depicted a strong association between HLA DR3/DR4 and islet autoimmunity of women with GDM.³¹ A similar observation was provided by Freinkel et al., showing a twofold increase in the frequency of DR3 and DR4 alleles in women with GDM.¹⁴ Ferber et al.⁹⁸ investigated 184 German women with GDM; when compared with another group of 254 nondiabetic unrelated subjects, no elevation in the frequency of any HLA class allele was observed. Nevertheless, DR3 allele frequency was increased in GDM women with positivity to islet cell antibodies, particularly GADA ($p = 0.002$), as well as DR4 and DQB1*0302 ($p = 0.009$). Those who had a DR3/DR4-containing genotype are 60% of women who are islet antibody positive and 74% of women who developed DM-1 postpartum. Combining the determination of susceptible HLA alleles (DR3, DR4) with islet AA measurement increased the sensitivity of identifying women with GDM developing postpartum DM-1 to 92%. Damm et al. showed a trend toward an increased frequency of DR3/DR4 and a decrease frequency of DR2 in women with GDM evolving to DM-1.³⁶ On the opposite, several reports could not find association between increased prevalence of class II alleles and the presence of humoral islet cell autoimmune markers in women with GDM.^{73,45,99}

C. Murgia et al., from the University of Cagliari, have reported a very high prevalence and very unusual distribution of antibodies in GDM patients of Sardinia (the population with the highest frequency of HLA DR3). They determined anti-GAD65, IA-2A, and IAA in a group of 62 GDM patients and in 56 controls. Frequency of AAs was 38.8% (7.1% for the control population), being IA-2A the most frequent antibody (29.0% in GDM patients, 7.1% in controls). The prevalence of GAD-65 AA was 3.2% (absent in controls). IAAs were positive in 14.5% of women with GDM (absent in controls). Eight percent of all GDM cases were positive for two antibodies (0% in controls).⁹⁸ Pregestational weight and BMI of DRA-positive GDM patients were lower than of DRA-negative GDM patients, in coincidence with other reports. One plausible explanation of these unique frequency and distribution of

pancreatic AAs among women presented with GDM in Sardinia is their distinct genetic background.

Anti-IA2 correlates with DQ8 and/or DR4/DQB1*0201 and is negatively associated with DR3/DQB1*02012; IAA and ICA are found with higher frequency in individuals positive for DR4 and DQ8, while anti-GAD65 is more commonly found in type 1 diabetic patients with DR3 and/or DQB1*0201 haplotypes.¹⁰⁰

Autoimmune GDM and LADA

S. Bo et al. investigated the differences in clinical characteristics of women with GDM, whether associated with islet cell autoimmunity or not.³⁵ A total of 207 women composed the total group of investigated subjects; 12.5% were carrying AAs in their sera, either ICAs or GADAs, usually at low titers. Women with GDM with autoimmune markers apparently presented a lower risk for the development of conventional GDM (were younger, had lower pre-pregnancy BMI, lower prevalence of diabetes in their FDRs, lower waist circumference, lower fasting plasma insulin, and lower weight increase during pregnancy). The rate of insulin treatment during pregnancy was significantly higher in the group positive for AAs. These observations led the authors to the conclusion that women with AIGDM

displayed fewer features of insulin resistance, required more frequent insulin therapy than negative women, and presumably had presymptomatic DM-1. Nevertheless, other authors have reported that women with GDM with or without GADA positivity at follow-up display similar clinical characteristics with the exception of BMI.⁵⁷

It may be hypothesized that women with AIGDM have LADA, which it has been demonstrated not to be the case. LADA is neither the same than classic DM-1A with onset in adulthood; although ICA and GADA are common in LADA, both anti-IA2 and IAA are much less common in LADA than in DM-1.¹⁰¹

Our group has recently reported the characteristics of LADA in Spanish population in terms of β -cell autoimmunity, insulin secretion, and clinical aspects.¹⁰² The study was initially part of the Action LADA Project, which was locally extended for an additional period of 3 years. Cases of LADA were defined as patients age 30–70 years at the diagnosis of diabetes, who did not require insulin for at least 6 months after diagnosis, with GADA or IA-2A positivity. A total of 82 consecutive patients with LADA, 78 patients with DM-1, and 480 patients with type 2 diabetes were included in the study. Table 7.2 shows the main clinical parameters of the three study groups. The investigation of metabolic characteristics depicted for patients with LADA an intermediate phenotype.

Table 7.2 Clinical characteristics, including fasting C-peptide concentrations of patients with type 1 diabetes, latent autoimmune diabetes in adults, or type 2 diabetes

	T1DM (n = 78)	LADA (n = 82)	T2DM (n = 480)	P value for group comparisons	
				T1DM—LADA	T2DM—LADA
Sex (n, women)	33 (42.3%)	30 (36.6%)	174 (36.3%)	0.518	1.000
Age (years)	45.5 ± 11.9	53.4 ± 12.3	56.07 ± 11.0	<0.001	0.076
Age at diagnosis	42.6 ± 11.4	49.2 ± 11.7	53.0 ± 10.5	<0.001	0.011
Disease duration (months)	10 (6–39)	38 (6–59)	24 (6–47)	<0.001	0.006
BMI (kg/m ²)	25.6 ± 4.92	26.9 ± 4.4	29.9 ± 5.4	0.031	<0.001
Waist (cm)	90.4 ± 12.5	94.8 ± 16.6	101.6 ± 14.4	0.003	<0.001
SBP (mmHg)	123.2 ± 24.0	131.4 ± 19.1	138.6 ± 21.5	0.036	0.002
DBP (mmHg)	74.0 ± 15.1	79.5 ± 9.9	82.3 ± 11.7	0.001	0.035
Antihypertensive treatment	11 (14.1%)	30 (36.6%)	248 (51.7%)	0.001	0.012
Triglycerides (mg/dL)	90.7 ± 48.4	121.5 ± 84.3	163.3 ± 120.8	0.022	<0.001
Total cholesterol (mg/dL)	192.4 ± 37.4	202.4 ± 61.6	218.8 ± 37.9	0.420	0.284
HDL cholesterol (mg/dL)	67.7 ± 23.2	59.8 ± 17.5	50 ± 15.8	0.037	<0.001
LDL cholesterol (mg/dL)	113.2 ± 33.5	118.7 ± 36.0	122.3 ± 35.5	0.321	0.192
Metabolic syndrome (n, %)	11 (15.5)	28 (37.3)	303 (67.2)	0.005	0.000
Fasting glycemia (mg/dL)	178.3 ± 80.7	164.8 ± 59.8	148.8 ± 56.3	0.529	0.010
HbA1c (%)	8.9 ± 2.7	8.1 ± 2.1	7.6 ± 1.9	0.098	0.007
C-peptide (pmol/L)	261.0 ± 234.0	587.0 ± 515.8	978.0 ± 480.7	<0.001	<0.001
Insulin treatment (alone or combined with other agents) (n, %)	78 (100.0)	37 (45.7)	91 (19.00)	<0.001	<0.001

Source: Mollo, A. et al., *Diabetes Metab. Res. Rev.*, 29, 446, 2013. With permission.

The prevalence of metabolic syndrome was higher among patients with LADA than in patients with T1DM, but lower in patients with T2DM. Fasting plasma glucose and HbA1c were higher in patients with LADA than in patients with T2DM. Hazard ratio for insulin treatment in LADA compared with T2DM was quite elevated (mean value of 8.34; $p < 0.001$). A faster progression to insulin treatment from the diagnosis of diabetes in patients with LADA when compared with patients with T2DM was clearly observed (Figure 7.1).

If immunotherapy becomes a reality for autoimmune diabetes, the investigation of both patients with LADA and women with AIGDM will be of great importance to identify subjects at high risk for T1DM who might benefit from immune intervention. New initiatives to be developed in these two distinct types of autoimmune diabetes—LADA and AIGDM—may include, among others, (1) the assessment of AAs to IA-2 β , which have been associated with a very high risk of diabetes in ICA/IA-2A-positive relatives of DM-1 subjects¹⁰³; (2) the use of the novel multi-antigen single radioimmunoassay, able to evaluate GADA, IA-2A, IAA, and islet beta-cell zinc cation efflux transporter (ZnT8) AAs¹⁰⁴; and (3) investigation of the humoral immunoreactivity against IA-2(256-760), the marker with the highest sensitivity for detection of humoral IA-2 immunoreactivity (IA-2 immunoreactivity has been underestimated, so far, in patients with LADA and AIGDM).¹⁰⁵ Furthermore, diagnosing LADA and AIGDM at the initial stage will be quite useful to initiate insulin earlier, facilitating improved glycemic control sooner as well as preserving the residual beta cell function in these two distinct subclasses of autoimmune diabetes.¹⁰⁶

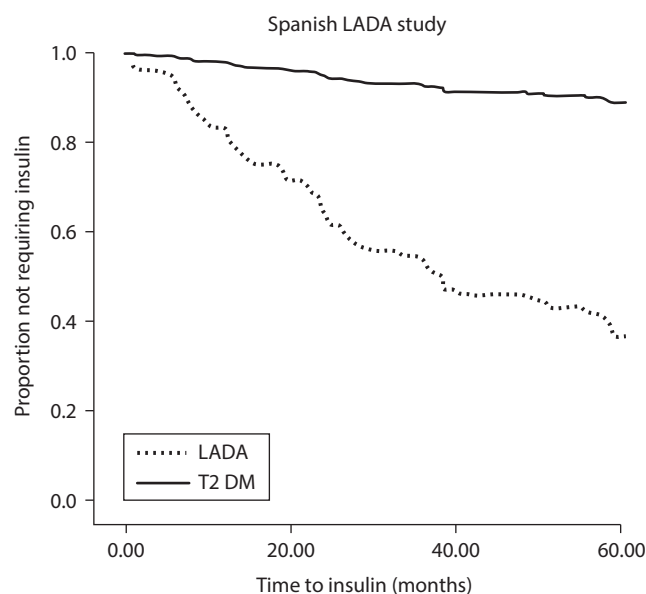


Figure 7.1 Spanish autoimmune diabetes of adulthood study. (From Molloy, A. et al., *Diabetes Metab. Res. Rev.*, 29, 446, 2013. With permission.)

GDM-related autoantibodies and the risk of maternal glucose intolerance/diabetes mellitus

The majority of reports have agreed that positivity for DRA during pregnancy increases the maternal risk of glucose intolerance/diabetes (Table 7.3).

In the first investigation on the prevalence of ICAs in GDM, three of five ICA (+) gestational diabetic women developed classic type 1A diabetes shortly after pregnancy.²⁶ Additional studies have confirmed an increased risk of diabetes³³ or glucose intolerance³⁰ in women positive for ICAs. The association has also been extended to other DRAs: positivity for either ICA/IA-2A or GADAs increases the risk of DM-1 2 years after delivery, with the risk increasing with the number of positive antibodies.²⁵

There are also articles reporting a lack of association of ICAs³² or GADAs⁵⁸ with abnormal glucose tolerance at short term after delivery that could be attributable to a low statistical power of the studies. Nevertheless, it is important to highlight that only two of these articles performed statistical adjustment for other predictors.^{25,32}

Our team have prospectively followed a group of 470 women with GDM from the time of diagnosis until the time of the first postpartum oral glucose tolerance test (OGTT), and up to 7 years afterward; another group of 200 women depicting normal OGTT at pregnancy, AAs negative, and similar age and BMI acted as control. Interestingly, the prevalence of all investigated AAs (ICA, GADA, IA-2A) markedly increased after delivery. In the systematic follow-up postpartum, the analysis of the curve of survival free of DM interval revealed an abrupt decline for the AA + group at the very early phase of the curve, remained afterward in a parallel fashion to the graphic displaying the behavior of the AA-negative group. In fact, about 80% of AA-positive women evolved to clinically overt diabetes within the first 24 months postpartum (Figure 7.2a and b). Investigators from the Munich Diabetes Research Institution also found increased risk of progression to DM in the group of AA+ women with GDM presenting DR3 and DR4 haplotypes. In this context, the association to GADA appears to have the strongest influence.²⁵

In addition to ICAs being predictive of diabetes at the first assessment after delivery,³³ our team reported an impairment of the acute insulin response to intravenous glucose in women with GDM with positivity for ICAs and normal glucose tolerance after delivery.¹⁰⁷ The response was superimposable to that of ICA(+) FDRs-DM-1 (Figure 7.3). Interestingly, a Finnish study on FDRs of patients with LADA demonstrated similar metabolic features that were described by us in women with GDM and positivity for ICAs. These individuals (family members of patients with LADA) exhibited decreased insulin secretion, associated with an increased prevalence of risk genotypes.¹⁰⁸

At longer follow-up, an increased risk of DM-1 has been demonstrated for ICA,^{27,29,36,47,109} GADA,^{27,54} and positivity

Table 7.3 Abnormal glucose tolerance at follow-up in women with gestational diabetes mellitus and diabetes-related antibodies

Author	Follow-up	ICAs	GADAs	IA-2As	Several DRAs
Steel et al. ²⁶	1 year	Predictive of type 1 diabetes			
Ginsberg-Fellner et al. ²⁹	Years	Predictive of type 1 diabetes			
Stowers et al. (1985)	Up to 22 years	Not predictive of the final state of glucose tolerance			
Catalano et al. ³⁰	Up to 4 years	Predictive of IGT			
Stangenberg et al. ³¹	2–4 months	Not predictive of abnormal OGTT ^a			
Mauricio et al. ³³	Months	Predictive of diabetes			
Damm et al. ³⁶	Up to 11 years	Predictive of type 1 diabetes			
Beischer et al. ⁵³	Years		GADAs at follow-up associated with type 1 and type 2 diabetes		
Petersen et al. ⁵⁴	Up to 11 years	Predictive of type 1 diabetes	Predictive of type 1 diabetes		DFJA positivity predictive of type 1 diabetes.
Fuchtenbusch et al. ²⁸	Up to 5 years	Predictive of type 1 diabetes ^a	Predictive of type 1 diabetes	Not predictive of type 1 diabetes ^a	Risk of type 1 diabetes increases with the number of DRAs. ^a
Panczel et al. ¹⁰⁹	Up to 14 years	Predictive of type 1 diabetes			
Kousta et al. ⁵⁷	Up to 45 months		GADAs at follow-up not associated with different FBG or HOMA estimations of insulin secretion and sensitivity		
Weng et al. ⁵⁸	1 year		No association with diabetes/IGT		
Lapolla et al. ³⁷	5 years				DRA positivity, borderline in association to type 1 diabetes.
Albareda et al. ⁴⁹	Up to 11 years				DRA positivity not predictive of diabetes, type 1 diabetes, or type 2 diabetes. ^a
Järvelä et al. (2006)	Up to 7 years	Predictive of type 1 diabetes ^a	Predictive of type 1 diabetes ^a	Not predictive of type 1 diabetes ^a	Number of DRAs predictive of type 1 diabetes. ^a
Löbner et al. ¹¹⁰	Up to 11 years				GAD and/or IA-2 positivity predictive of diabetes. ^a

Source: de Leiva, A. et al., *Diabetes Care*, 30(Suppl. 2), 127, 2007. With permission.

Note: For groups with several articles on the subject, only articles providing new information on the predictive ability of diabetes-related antibodies are included.

Abbreviations: FBG, fasting blood glucose; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

^a Adjusted for other predictors.

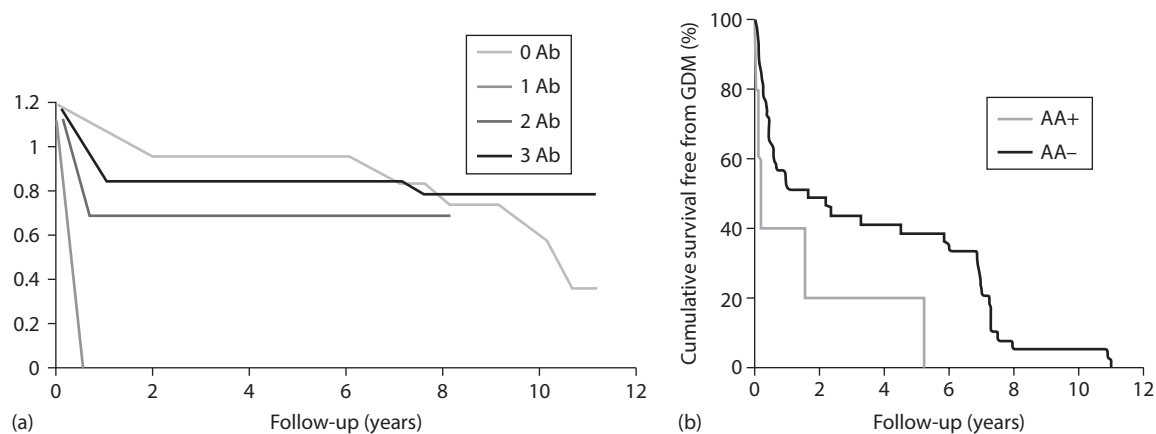


Figure 7.2 (a) GDM: progression to DM at postpartum follow-up. (b) Gestational diabetes mellitus (GDM): cumulative survival free from GDM. ([a] Adapted from Mauricio, D. et al., *Diabetes Metab. Res. Rev.*, 17(6), 422, 2001; [b] modified from Albareda, M. et al., *Diabetologia*, 41, 106, 1998.)

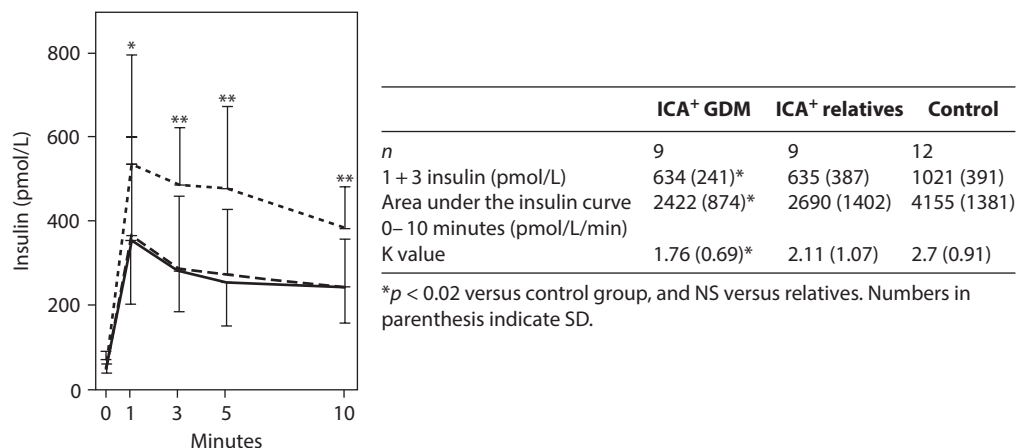


Figure 7.3 Gestational diabetes mellitus: islet cell autoantibody, IVGTT, insulin release. (From Mauricio, D. et al., *Diabet. Med.*, 12, 1009, 1995. With permission.)

for one or more islet cell antibodies,^{54,110–112} with the risk increasing with the number of antibodies,²⁷ but not for IA-2.^{25,27} Even for ICAs and GADAs, not all articles find a positive association between DRA positivity and diabetes at follow-up, which in some cases,^{28,27} but not others,^{49,57} can be attributed to a low statistical power. For example, in our population, despite the aforementioned association of ICA positivity with postpartum abnormal glucose tolerance, DRA positivity (ICA/GADA/IA-2, alone or in any combination) was not predictive of diabetes at midterm follow-up.⁴⁹ As in the case of short-term follow-up, only some studies have adjusted for other predictors^{27,49,110}

In our opinion, the beta-cell secretory capacity of an otherwise normal glucose-tolerant woman may be challenged by the higher functional demand associated with the state of pregnancy. After delivery, the autoimmune process may follow different pathways. One would be that of the restoration of normal glucose tolerance when pregnancy is over, with eventual persistence or disappearance

of autoimmune markers. This has already been observed in FDRs of type 1 diabetic subjects. Another possibility points to the appearance of DM-1 shortly after pregnancy. Alternatively, progression to an established state of glucose intolerance could occur, which may eventually progress to further deterioration of the insulin-secretory capacity as a result of the progression of autoimmune destruction of beta cells. If the autoimmune process evolves, the time course and degree of destruction may vary. This can result in a full and rapid progression to late-onset DM-1, with the typical onset of the disease. Alternatively, the process may progress slowly, resulting in a long subclinical period with further progression to a non-insulin-dependent state manifested as LADA. Moreover, the course of the autoimmune destruction of the beta-cell mass may be accelerated at any time point in patients with LADA resulting in a rapid-onset insulin-dependent form of DM-1 (Figure 7.4).²⁵

These considerations were accepted by the Consensus Panel at the *Fifth International Workshop-Conference on*

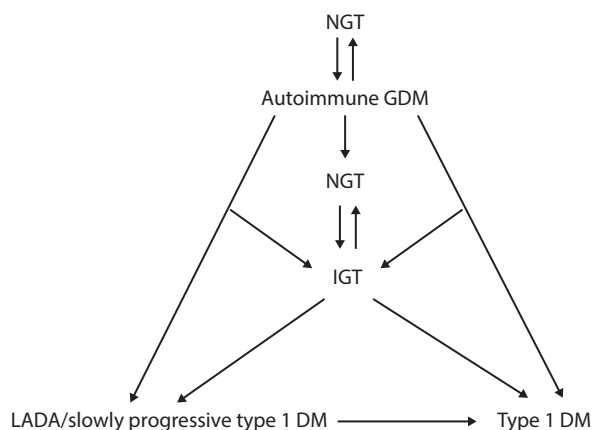


Figure 7.4 Autoimmunity in gestational diabetes mellitus: postpartum follow-up. (From Mauricio, D. et al., *Diabetes Metab. Rev.*, 12, 275, 1996. With permission.)

GDM (Chicago, 2007). In the final report of the conference, it was included the proposal that women with GDM depicting AA should be subjected during the follow-up to a closer surveillance due to their high risk to develop rapid progression to insulinopenic diabetes.¹¹³ Theoretically, this subgroup of women can be clearly considered as prediabetic type 1. Although initiatives to prevent DM-1 have been unsuccessful so far, AA-associated GDM means a distinct category of candidates for such purpose. One illustration of the need that women with GDM depicting AA should be closely followed during pregnancy has been shown by the group of DM and pregnancy of the University of Padova, reported in 2013. Three women attended either at pregnancy or at the postpartum displayed high GAD antibodies titers. They developed persistent autoimmune diabetes requiring insulin treatment (two of them during pregnancy and the third after partum).¹¹⁴

Autoimmune GDM: A distinct prediabetic stage

Approximately, 10% of women with GDM displays humoral autoimmune markers against pancreatic cells in association with glucose intolerance at pregnancy.

Freinkel et al.²⁴ foresaw the evolution of what may be defined as AIGDM, when they wrote in 1987, that GDM entails genotypic and phenotypic diversity and may include

patients with slowly evolving DM-1. We consider that this condition may display the various types of expression of the immune reactivity against the β -cell. AIGDM appears to be the result of the variable expression of autoimmunity against the beta cell, challenged by the higher functional demand associated with the insulin-resistant state of pregnancy.¹¹⁵

There are different time-course patterns in the progression of AIGDM: from the restoration of normal glucose tolerance when pregnancy is over (even with eventual disappearance of autoimmune markers) to the appearance of DM-1 shortly postpartum, to an established state of glucose intolerance that may eventually progress slowly, and to a non-insulin-dependent state, manifested as LADA. Furthermore, the course of the autoimmune destruction of the residual beta cell mass may be accelerated at any time point resulting in a rapid-onset form of DM-1.

With these considerations, we have proposed that AIGDM be regarded as a distinct clinical entity.¹¹⁵ This proposal does not only make reference to a special subtype of GDM for academic or classification purposes, but it also addresses a peculiar and complex prediabetic status, susceptible of future new strategies for diabetes prevention. Due to its potential high risk for progression to clinically overt insulinopenia, women with AIGDM may be considered candidates for immune interventions.

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8 Epidemiology of gestational diabetes mellitus

Yariv Yogeve, Avi Ben Haroush, Moshe Hod, and Jeremy Oats

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or is first recognized during pregnancy.¹ Although it is a well-known cause of pregnancy complications, a systematic review of its epidemiology has become more complex following the introduction of new World Health Organization (WHO)/International Association Diabetes in Pregnancy Study Group (IADPSG) international criteria that are for the first time based on the risk of adverse perinatal outcomes.² A further problem is the distinction of GDM from preexisting but undiagnosed diabetes, so that the degree of clinical surveillance may have a major impact on the estimated prevalence of GDM in a given population. This is especially true in high-risk populations in which the onset of type 2 diabetes mellitus (type 2 DM) occurs at an early age.³ Further, investigators have used different screening programs and diagnostic criteria for GDM, making comparisons among studies difficult.

In this chapter, the reported risk factors for GDM, differences in its racial distribution, and evidence of a genetic or familial association will be discussed. These differences may well need to be further reviewed as studies using the new criteria become available. The close relationship of GDM to polycystic ovarian syndrome (PCOS), the aspects of the associations between GDM and adverse pregnancy outcomes, including congenital anomalies, and the risk of type 2 DM will also be described.

Racial distribution of gestational diabetes mellitus

The International Diabetes Federation recently estimated that 16.6% of live births to women in 2013 had some form of hyperglycemia during the pregnancy of which 16% were GDM using the new criteria.⁴ There were major regional differences ranging from 25.0% in Southeast Asian region to 10.4% in North America and the Caribbean region. Of concern, 91.6% of cases were in low- and middle-income countries where access to maternity care can be problematic. The prevalence by international diabetes foundation (IDF) region is shown in Table 8.1.

The prevalence of GDM varies in direct proportion to the prevalence of type 2 DM in a given population or ethnic group.¹ The reported prevalence of GDM in the United States ranges from 1% to 14%, with 2% to 5% being the most common rate.⁵ In an earlier report, using previous WHO criteria, on the prevalence of diabetes and impaired glucose tolerance (IGT) in diverse populations in women between the ages of 20 and 39, the WHO Ad Hoc Diabetes Reporting Group⁶ noted lower rates of diabetes (<1%) in Bantu (Tanzania), Chinese rural Indian, Sri Lankan, and some Pacific populations followed (1%–3%) by Italian women and white, black, and Hispanic women in the United States. Rural Fijian Indian and Aboriginal Australian women had 7% prevalence; the highest rate was found in Pima/Papago Indians and Nauruans (14%–22%). The prevalence of IGT was low (<3%) in Chinese and Malays and was >10% in black and Hispanic women in the United States, urban Indian women in Tanzania, Pima and Nauruan, and some other Pacific communities. The combined age-standardized prevalence of diabetes and IGT ranged from 0% to 36%, with a >10% prevalence in one-third of the populations and a >30% prevalence in Pima and Nauruan. Importantly, in some populations, more than half of the cases of diabetes were undiagnosed prior to the survey. IGT was mostly overlooked in routine clinical practice. This, a substantial proportion of abnormal glucose tolerance in pregnancy, will be undetected without screening.

When analyzing these older studies, it is important before concluding that there are necessarily marked racial and geographic variations in the prevalence of GDM, to make allowance for the remarkably variable approaches used across different studies, including different methods of screening, different oral glucose and intravenous glucose loads, and different diagnostic criteria. For example, Dooley et al.⁷ demonstrated that race as well as maternal age and degree of obesity must be taken into account in comparing the prevalence of GDM in different populations. Their study included 3744 consecutive pregnant women who underwent universal screening. The population was 39.1% white, 37.7% black, 19.8% Hispanic, and 3.4% oriental/other. Black and Hispanic race, maternal age, and percentage ideal body weight had a significant independent effect on the prevalence of GDM. The adjusted relative risk (RR) was higher in black

Table 8.1 Hyperglycemia in pregnancy (20–49 years) by IDF Region, 2013

IDF region	Cases in live births (millions)	Comparative prevalence (%)
Africa	4.6	14.4
Europe	1.7	12.6
Middle east and North Africa	3.4	17.5
North America Caribbean	0.9	10.4
South and Central America	0.9	11.4
Southeast Asia	6.3	25.0
Western Pacific	3.7	11.9

Source: International Diabetes Federation, *IDF Diabetes Atlas*, 6th ed., IDF, Brussels, Belgium, 2013.

(1.81 95% confidence interval [CI] 11.13–2.89) and Hispanic (2.45, 95% CI 1.48–4.04) women than in white women. The degree of carbohydrate intolerance was similar across racial groups; nevertheless, when the 92 patients with GDM under dietary control were analyzed separately, mean birth weight was found to be highest in Hispanic women and was lowest in the blacks and Orientals. Hence, race had a significant independent effect on birth weight, with percentage ideal body weight a significant covariant. These findings are supported by Gunton et al.⁸ who showed Asian women were more likely to have GDM than Caucasian women (31.7% vs. 14%, $p = 0.02$), despite their lower body mass index (BMI).

Although the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study⁹ was not a population study, when the WHO/IADPSG criteria were applied to the glucose tolerance test (GTT) results, there were marked differences in the prevalence of GDM across the 15 field centers in 9 different countries. The overall prevalence was 16.1%, rates ranged from 8.7%

in Beersheba, Israel, 9.9% in Barbados, West Indies, to 21% in Manchester, United Kingdom, and 23.7% Cleveland, United States (Table 8.2).¹⁰

Risk factors for gestational diabetes mellitus

The traditional and most often reported risk factors for GDM are high maternal age, weight and parity, previous delivery of a macrosomic infant, and a family history of diabetes. These and other reported risk factors are summarized in Table 8.2. It is of great importance that the clinician understand and use these characteristics, along with others, such as racial and geographic attributed risk (discussed earlier), to improve screening programs and diagnostic accuracy and perhaps to design better and more cost-effective selective screening and diagnostic tests.

Table 8.2 Frequency of gestational diabetes mellitus by hyperglycemia and adverse pregnancy outcome field center using World Health Organization/IADPSG criteria

Field center	No. participants	Percent with GDM
<i>HAPO overall</i>	<i>23,316</i>	<i>16.1</i>
Cleveland, USA	784	23.7
Bellflower, USA	1,903	22.9
Singapore	1,695	22.4
Bangkok, Thailand	2,426	21.2
Manchester, U.K.	2,250	21.0
Chicago, USA	738	16.5
Belfast, U.K.	1,634	15.5
Toronto, Canada	1,988	14.6
Providence, USA	746	14.2
Newcastle, Australia	653	13.6
Hong Kong, China	1,620	13.4
Brisbane, Australia	1,437	12.1
Barbados, West Indies	2,034	9.9
Petah Tikva, Israel	1,798	9.2
Beersheba, Israel	1,610	8.7

Source: Sacks, D.A. et al., *Diabetes Care*, 35, 526, 2012.

Jang et al.¹¹ examined 3581 consecutive Korean women and found a 2.2% prevalence of GDM. The affected women were older and had higher prepregnancy weights, higher BMI, higher parity, and higher frequencies of known diabetes in the family. The risk of diabetes was closely associated with previous obstetric outcome, such as congenital malformation, stillbirth, and macrosomia. The number of risk factors present in each individual increased the risk of diabetes, with the prevalence ranging from 0.6% in subjects without any risk factors to 33% in those with four or more. Thus, it is possible that selective screening may be cost-effective in situations where health resources are scarce and where total screening is impossible.²

Similar results were reported in a retrospective cohort study of 2574 pregnant women, which suggested that elective screening programs have a true-positive yield.¹² An age of ≥ 30 , a family history of diabetes, obesity ($\text{BMI} \geq 27$), and previous fetal macrosomia were the most important risk factors. Just over half (54.2%) of the population present with one or more risk factors. The positive predictive value of screening increased with the number of risk factors, from 12% for the women with no risk factors to 40% for those with three or more risk factors.

In another study, Jang et al.¹³ demonstrated that in the racially homogeneous population of Seoul, Korea, besides prepregnancy BMI, age, weight gain, and parental history of diabetes, short stature is an independent risk factor for GDM. Accordingly, Kousta et al.¹⁴ reported that European and South Asian women with previous GDM were shorter than control women from the same ethnic groups, perhaps due to a common pathophysiological mechanism underlying GDM and the determination of final adult height. Others have reported similar results.¹⁵

In a large retrospective cohort study in Canada, Xiong et al.¹⁶ evaluated 111,563 pregnancies and detected a 2.5% prevalence of GDM. The risk factors identified were age > 35 years, obesity, history of prior neonatal death, and a prior cesarean section. Interestingly, teenage mothers and women who drank less alcohol were less likely to have GDM.

The risk factors mentioned earlier are mainly of maternal origin. However, cumulative knowledge about the long-term implications of exposure to the diabetic intrauterine environment (see Chapter X) has led to the addition of the mother's fetal history to the risk factor list. Egeland et al.¹⁷ investigated whether the mother's own characteristics at birth could predict her subsequent risk of GDM. Using linked generation data from the Medical Birth Registry of Norway for all women born between 1967 and 1998, the authors identified 498 women aged < 32 years with GDM in one or more singleton pregnancies. They found that the women whose mothers had diabetes during pregnancy were at increased risk of GDM themselves. Significant inverse trends in diabetes were noted in relation to birth weight, with an increased risk of GDM of 80%, 60%, and 40% in women whose birth weights were ≤ 2500 , 2500–2999, and 3000–3499 g, respectively, compared with women in the 4000–4500 g group. Similar findings were observed for categories of weight for gestational age.

Is GDM a cause or an effect? A retrospective study in Hong Kong¹⁸ in 84 normotensive women showed that the progressive glucose intolerance throughout pregnancy is associated with an upward shift in blood pressure in the third trimester. Hence, it is possible that blood pressure changes below the diagnostic threshold for hypertensive disorders of pregnancy may help identify women at increased risk of GDM.

The relationship between dietary fat and glucose metabolism has been recognized for many years. Epidemiological data in humans suggest that subject with a higher fat intake are more prone to disturbances in glucose metabolism.¹⁹ Several researchers have hypothesized that polyunsaturated fatty acid plays an essential role in the maintenance of energy balance and, through regulation of gene transcription, may improve insulin resistance.^{20–22} A recent small study reported significantly lower cord vein erythrocyte phospholipid fatty acid concentrations in 13 women with GDM compared with 12 women with normal pregnancies.²³ Accordingly, Bo et al.²⁴ investigated the relationship between lifestyle habits and glucose abnormalities in 504 Caucasian women with and without conventional risk factors for GDM. They identified 126 women with GDM and 84 with IGT. These women were older and shorter than the women with normal pregnancies and had significantly higher prepregnancy BMI, higher rates of diabetes in first-degree relatives, and higher intakes of saturated fat. In a multiple logistic regression model, all of these factors were associated with glucose abnormalities, after adjustment for gestational age. In the patients without conventional risk factors, only the percentage of saturated fats (odds ratio [OR] = 2.0, 95% CI 1.2–3.2) and polyunsaturated fats (OR = 0.85, 95% CI 0.77–0.92) were associated with gestational hyperglycemia, after adjustment for age, gestational age, and BMI. Thus, the allegedly independent role of saturated fat in the development of gestational glucose abnormalities takes on greater importance in the absence of conventional risk factors. This suggests that glucose abnormalities could be prevented in some groups of women during pregnancy.

A possible expression of the still unknown genetic linkage in GDM was reported by Lao and Ho,²⁵ who detected GDM in 62% of 163 women with the alpha-thalassemia trait compared to 14.7% out of 163 controls matched for age and parity.

Polycystic ovary syndrome and gestational diabetes mellitus

PCOS is a heterogeneous disorder affecting 5%–10% of women of reproductive age. It is characterized by chronic anovulation with oligo-/amenorrhea, infertility, typical sonographic appearance of the ovaries, and clinical or biochemical hyperandrogenism. Insulin resistance is present in 40%–50% of patients, especially in obese women.²⁶

Holte et al.²⁷ reported a higher rate of ultrasonographic, clinical, and endocrine signs of PCOS in 34 women who had had GDM 3–5 years before, compared to 36 matched

controls with uncomplicated pregnancies. Five of the women (15%) with previous GDM had developed manifest diabetes. The authors concluded that in women with previous GDM, PCOS may form a distinct subgroup from women with normal ovaries and previous GDM, who may be more prone to develop features of insulin resistance syndrome.

Many other researchers reported similar results, Kousta et al.²⁸ found a higher prevalence of PCOS in 91 women with previous GDM compared to 73 normoglycemic control women (52% vs. 27%, $p = 0.002$), and Anttila et al.²⁹ reported a 44% prevalence of PCOS in women with GDM, with no differences in BMI before pregnancy or in weight gain during pregnancy compared to controls. They suggested a screening program for GDM in these patients.

Mikola et al.³⁰ retrospectively evaluated 99 pregnancies in women with PCOS compared with an unselected control population. The average BMI and the nulliparity rate were higher in the PCOS group, as was the multiple pregnancy rate (9.2% vs. 1.1%). GDM developed in 20% of the patients with PCOS but in only 8.9% of the controls ($p < 0.001$). A BMI >25 was the best predictor of GDM (adjusted OR = 5.1, 95% CI 3.2–8.3), and PCOS was an additional independent predictor (adjusted OR = 1.9, 95% CI 1.0–3.5).

Koivunen et al.³¹ found that compared with 48 control women, 33 women with previous GDM more often had significantly abnormal oral glucose tolerance tests (OGTT); higher prevalences of polycystic ovaries (39.4% vs. 16.7%, $p = 0.03$); higher serum concentrations of cortisol, dehydroepiandrosterone, and dehydroepiandrosterone sulfate; and a greater area under the glucose curve.

Multiple pregnancy and gestational diabetes mellitus

The number of fetuses in multifetal pregnancies is expected to influence the incidence of GDM owing to the increased placental mass and, thereby, the increase in diabetogenic hormones. However, the reports are somewhat conflicting, probably because of the heterogeneous populations studied.

In an interesting study of the prevalence of GDM in dizygotic (DZ) twin pregnancies with two placentas compared to monozygotic (MZ) twin pregnancies with one placenta, Hoskins³² evaluated 3458 recorded twin deliveries and found a higher proportion of different sex compared with same-sex twin pregnancies complicated by GDM (3.5% vs. 1.6%). The estimated risk for DZ twin pregnancies relative to MZ pregnancies was 8.6 (95% CI 3.5–21.0). The impact of fetal reduction on the incidence of GDM may support this theory. Sivan et al.³³ examined 188 consecutive triplet pregnancies of which 85 were reduced to twins. The rate of GDM was significantly higher in the triplet group than in the reduction group (22.3% vs. 5.8%).

Similar results were reported by Schwarz et al.³⁴ in a study of 29,644 deliveries. They found that GDM was significantly more frequent in the 429 twin deliveries (7.7% vs. 4.9%, $p < 0.05$). However, insulin requirements were not

different, suggesting a minor clinical impact. Wein et al.³⁵ compared the prevalence of GDM between 61,914 singleton and 798 twin deliveries performed between 1971 and 1991. The difference was significant only for the earlier decade (5.6% vs. 7.4%, $p = 0.025$). However, in a follow-up program, there was a trend toward higher prevalence of overt diabetes in women who had a diabetic twin pregnancy (18.5%) compared to those who had a diabetic singleton pregnancy (7.4%). Whether this represents a true increased risk for diabetes is unknown.

By contrast, using data derived from the Medical Birth Registry of Norway, Egeland and Irgens,³⁶ controlling for other risk factors such as advance age, parity, maternal history of diabetes, and the woman's own birth weight, found GDM in 6.6 per 1000 multiple pregnancies ($n = 9,271$) and in 5.0 per 1000 singleton pregnancies ($n = 640,700$) (OR = 1.3 95% CI 1.0–1.7, $p = 0.03$). However, analysis stratified by maternal age or parity yielded no elevated risk of GDM. Others have also failed to demonstrate a higher prevalence of GDM in multiple pregnancies.^{37,38}

Genetic factors

Animal studies have shown that female fetuses exposed to a diabetic intrauterine milieu have an increased risk of subsequent GDM. In a family history study, Harder et al.³⁹ reported a significantly greater prevalence of diabetes (mainly type 2 DM) in the mothers of women with GDM than in their fathers. A significant aggregation of type 2 DM was also observed in the maternal–grandmaternal line compared to the paternal–grandpaternal line. However, in patients with IDDM, there was no significant difference in the prevalence of any type of diabetes between mothers and fathers. Therefore, a history of type 2 DM on the mother's side might be considered as a particular risk factor for GDM via “intergenerational transmission of type 2 DM,” which might be prevented by strict avoidance of GDM.

Dorner et al.⁴⁰ reported a significantly decreased familial diabetes aggregation on the maternal side in children with type 1 DM born between 1974 and 1984 compared to those born between 1960 and 1973. This finding was explained by the improved prevention of hyperglycemia during pregnancy since 1974 and particularly of GDM in women with familial diabetes aggregation. These authors also noted a highly significant predominance of type 2 DM in the great-grandmothers of individuals with type 1 DM compared to the paternal side. They suggested that GDM, which may represent a risk factor for diabetes transmission on the maternal side, is often followed by “extragenerational” type 2 DM at a later age. Like Harder et al.,³⁹ these authors suggested that their findings were consistent with the suspected teratogenic effect of GDM on diabetes susceptibility in the offspring and that this was preventable by avoiding hyperglycemia in pregnant women and hyperinsulinism in fetuses.

Histocompatibility leukocyte antigen (HLA) studies are one way to establish a genetic linkage in certain diseases. In GDM, conflicting results have been reported. Kuhl⁴¹ described

similar frequencies of HLA DR2, DR3, and DR4 antigens in healthy pregnant women and women with GDM and low prevalences of markers of autoimmune destruction of the beta cells in GDM pregnancies. Likewise, Vambergue et al.,⁴² in a study of 95 women with GDM, 95 with IGT, and 95 control pregnant women, found no significant difference in the distribution of HLA class II polymorphism among the groups. However, the GDM and IGT groups presented some particular HLA patterns, pointing to a genetic heterogeneity of glucose intolerance in pregnancy.

Lapolla et al.⁴³ evaluated 68 women with GDM and matched controls for the frequency of HLA A, B, C, and DR antigens; the only significant differences were an increase in Cw7 and a decrease in A10 in the GDM group. Budowle et al.⁴⁴ reported that the Bf-F allele was found significantly less frequently in nonobese black women with GDM compared to controls and suggested similar genetic associations in nonobese black women with GDM and type 2 DM. Similarly, in another study, women with GDM who required insulin for glycemic control had a lower frequency of the Bf-F phenotype and a higher frequency of the Bf-f1 phenotype; they also had a lower frequency of the type 2 allele at the polymorphic locus adjacent to the insulin gene.⁴⁵

Freinkel et al.⁴⁶ evaluated 199 women with GDM and 148 patients with normal pregnancies and found that HLA DR3 and DR4 antigens occurred significantly more often in black women with GDM. Ferber et al.,⁴⁷ in an analysis of 184 women with GDM, did not find an elevation in the frequency of any HLA II alleles in the GDM patients compared with nondiabetic unrelated subjects. However, the DR3 allele was noted significantly more frequently in 43 women with islet autoantibodies and in the 24 women who developed type 1 DM postpartum. The cumulative risk of developing type 1 DM within 2 years after pregnancy in the women with GDM with DR3 or DR4 was 22% and in the women without these alleles was 7% ($p = 0.02$). The risk rose to 50% in the DR3- and DR4-positive women who had required insulin during pregnancy ($p = 0.006$). These results indicate that women with GDM who have islet autoantibodies at delivery or develop type 1 DM postpartum have HLA alleles typical of late-onset type 1 DM and that both HLA typing and islet antibodies can predict the development of type 1 DM postpartum.

Recurrence of gestational diabetes mellitus

MacNeill et al.⁴⁸ conducted a retrospective longitudinal study of 651 women who had had a diabetic pregnancy and at least one other thereafter. They found a 35.6% recurrence rate of GDM. Multivariate regression models showed that infant birth weight in the index pregnancy and maternal weight before the subsequent pregnancy were predictive of recurrent GDM.

Higher recurrence rates (69% of 78 patients) were reported by Major et al.⁴⁹ Recurrence was more common when the

following variables were present in the index pregnancy: parity ≥ 1 (OR = 3.6), BMI ≥ 30 (OR = 3.6), GDM diagnosed ≤ 24 weeks gestation (OR = 20.4), and insulin requirement (OR = 2.3). A weight gain ≥ 7 kg (c. 15 lb) (OR = 2.9) and an interval between pregnancies of ≤ 24 months (OR = 1.6) were also associated with a recurrence of GDM. Spong et al.⁵⁰ found a similarly high recurrence rate of 68% in 164 women with GDM. Risk factors for recurrence in this study were earlier diagnosis of GDM, insulin requirement, and hospital admissions in the index pregnancy.

Abnormal glucose tolerance test as a risk factor for adverse pregnancy outcome

The relationships between maternal hyperglycemia measured during a 75 g OGTT administered early in the third trimester of pregnancy and adverse pregnancy outcome have been clearly demonstrated by the HAPO study.⁹ The adjusted ORs were calculated for adverse pregnancy outcomes associated with an increase in the fasting plasma glucose level of 1 SD (6.9 mg/dL [0.4 mmol/L]), an increase in the 1-hour plasma glucose level of 1 SD (30.9 mg/dL [1.7 mmol/L]), and an increase in the 2-hour plasma glucose level of 1 SD (23.5 mg/dL [1.3 mmol/L]). For birth weight above the 90th percentile, the ORs were 1.38 (95% CI, 1.32–1.44), 1.46 (1.39–1.53), and 1.38 (1.32–1.44), respectively; for cord blood serum C-peptide level above the 90th percentile, 1.55 (95% CI, 1.47–1.64), 1.46 (1.38–1.54), and 1.37 (1.30–1.44); for primary cesarean delivery, 1.11 (95% CI, 1.06–1.15), 1.10 (1.06–1.15), and 1.08 (1.03–1.12); and for neonatal hypoglycemia, 1.08 (95% CI, 0.98–1.19), 1.13 (1.03–1.26), and 1.10 (1.00–1.12).

Likewise there were significant continuous relationships for the secondary outcomes, the strongest being preeclampsia followed by shoulder dystocia and birth trauma where for each 1SD rise the ORs ranged from 1.21 to 1.28 and 1.20 across the three glucose measurements, respectively. Premature delivery, the requirement for an increased level of neonatal care, and treatment for hyperbilirubinemia were all related to the 1- and 2-hour postload levels, but not fasting glucose. Importantly, these relationships were independent of maternal BMI, age, family history of diabetes, gestational age at OGTT, infant sex, mean arterial pressure at OGTT, and hospitalization for complications of pregnancy.

Early gestational diabetes mellitus diagnosis as a risk factor

Early onset of GDM is a high-risk factor. Bartha et al.⁵¹ found that among 3986 pregnant women, those with early-onset GDM ($n = 65$) were more likely to be hypertensive (18.46% vs. 5.88%, $p = 0.006$) and have higher glycemic levels and greater needs for insulin therapy (33.85% vs. 7.06%, $p < 0.001$) than

those in whom diabetes developed later ($n = 170$). All cases of neonatal hypoglycemia ($n = 4$) and all perinatal deaths ($n = 3$) were in this group. The women with early-onset GDM also had an increased risk of postpartum DM, whereas those with late-onset GDM had a minimal risk.⁵² The percentages of overt diabetes and abnormal glucose tolerance were significantly higher in the early-pregnancy group ($n = 30$) than in the late-pregnancy group ($n = 72$) (26.7% vs. 1.4% and 40% vs. 5.56% respectively).

Congenital malformations

Schaefer-Graf et al.⁵³ in a review of 4180 pregnancies complicated by GDM ($n = 3764$) or type 2 DM ($n = 416$), reported that the congenital anomalies in the offspring affected the same organ systems described in pregnancies complicated by IDDM. The risk of anomalies rose with the increasing hyperglycemia at diagnosis or presentation for care. However, most other reports had conflicting findings. Bartha et al.⁵¹ failed to find an increase in major congenital malformations associated with GDM, as did Kalter⁵⁴ in a comprehensive review of the literature. An exception is the recent Swedish Health Registry study covering over 1.2 million births between 1987 and 1997.⁵⁵ The author identified 3864 infants born to women with preexisting diabetes and 8688 infants born to women with GDM. The total malformation rate in the first group was 9.5% and in the second group 5.7%, similar to the rate in the general population. However, the GDM group was characterized by an excess of certain malformations, suggesting that a subgroup of GDM are at increased risk of diabetic embryopathy, perhaps due to preexisting but undetected type 2 DM.

Martinez-Frias et al.⁵⁶ analyzed 19,577 consecutive infants with malformations of unknown cause and compared those born to mothers with GDM with those of nondiabetic mothers. Their findings indicated that GDM is a significant risk factor for holoprosencephaly, upper/lower spine/rib anomalies, and renal and urinary system anomalies. However, owing to the heterogeneous nature of GDM, which includes previously unrecognized and newly diagnosed type 2 DM, they could not rule out the possibility that the teratogenic effect is related to latent type 2 DM. Nevertheless, they concluded that pregnancies complicated by GDM should be considered at risk for congenital anomalies.

By contrast, the relationship between GDM and the development of congenital malformations was examined in another population-based retrospective study using birth certificate data for all live-born children delivered between 1984 and 1991 in Washington State.⁵⁷ The prevalence of congenital malformations was 7.2%, 2.8%, and 2.1% among offspring of mothers with established diabetes ($n = 8869$), with GDM ($n = 1511$) and without diabetes ($n = 8934$), respectively. That is, the rate of congenital malformations in the GDM group was only slightly higher than in the control group (OR = 1.3, 95% CI 1.0–1.6).

Hypertensive disorders

Preeclampsia and gestational hypertension are apparently more frequent in women with GDM. As noted earlier, the HAPO study demonstrated a strong association between increasing maternal glucose levels and preeclampsia. A large study by Xiong et al.¹⁶ detected preeclampsia in 2.7% of 2,755 patients with GDM compared with only 1.1% of 108,664 patients with normal pregnancies (adjusted OR = 1.3, 95% CI 1.20–1.41). Similar results were observed for gestational hypertension. Likewise Dukler et al.⁵⁸ studied 380 primiparous women with preeclampsia and 385 primiparous control women for a total of 121,207 and 1,293 deliveries, respectively. When adjusted for confounding variables, GDM was strongly associated with the recurrence of preeclampsia in the second pregnancy (OR = 3.72, 95% CI 1.45–9.53).

Further evidence for the relationship between GDM and preeclampsia comes from the two RCTs of treatment of GDM—the ACHOIS⁵⁹ and Landon and colleagues.⁶⁰

In the ACHOIS study,⁵⁹ the incidence of preeclampsia was reduced from 18% to 12% from the controls to the treatment group (adjusted treatment effect 0.70 [95% CI 0.51–0.95]).

In the Landon study,⁶⁰ the incidence of preeclampsia in the treatment group was 2.5% compared with 5.5% for the controls (RR 0.46, 97% CI 0.22–0.97).

Go et al.,⁶¹ in an 11-year follow-up study of a cross-sectional sample of African-American women with a history of GDM ($n = 289$), reported one of the highest rates of microalbuminuria (MA) of all ethnic groups. The presence of MA was not associated with insulin resistance, but it was significantly and independently associated with glycosylated hemoglobin (HbA1c) levels and hypertension. Hence, hypertension and glucose tolerance influence MA through different mechanisms, and screening for MA should be considered in this patient population.

Conditions associated with increased insulin resistance, such as GDM, PCOS, and obesity, may predispose patients to essential hypertension, hypertensive pregnancy, hyperinsulinemia, hyperlipidemia, and high levels of plasminogen activator inhibitor-1, leptin, and tumor necrosis factor- α . These findings may also be associated with cardiovascular complications in these women.⁶² Joffe et al.⁶³ provided further support for the role of insulin resistance in the pathogenesis of hypertensive disorders of pregnancy. In a prospective study of 4589 healthy nulliparous women, they found that the women with GDM had an increased RR of preeclampsia and all hypertensive disorders (RR = 1.67, 95% CI 0.92–3.05 and RR = 1.54, 95% CI 1.28–2.11 respectively). RR were not substantially reduced after further adjustment for race and BMI (OR = 1.41 and 1.48, respectively). Furthermore, even within the normal range, multivariate analysis demonstrated that the level of plasma glucose 1 hour after a 50 g oral glucose challenge was an important predictor of preeclampsia.

Innes et al.⁶⁴ evaluated 54 normotensive women who developed hypertension in pregnancy and 51 controls with normotensive pregnancies, matched for parity. Mean

postload glucose levels and the total glucose area under the curve were significantly higher in the cases than the controls and were positively correlated with peak mean arterial pressure. After adjustment for potential confounders, 2-hour postload glucose levels remained strongly related to the risk for hypertension and to peak mean arterial pressure, as did the total area under the curve. The cases were also more likely to have had one abnormal OGTT. Stratifying analyses by case severity (preeclampsia and gestational hypertension) yielded similar results. Among all subjects, more cases than controls were also diagnosed with GDM (31% vs. 12%, $p = 0.008$).

Risk of type 2 diabetes mellitus

Women with GDM have a 17%–63% risk of type 2 DM within 5–6 years.⁶⁵ However, the risk varies according to different parameters. For example, Greenberg et al.⁶⁶ reported that the most significant predictor of 6 weeks postpartum diabetes was insulin requirement, with RR = 17.28 (95% CI 2.46–134.42) followed by poor glycemic control, glucose tolerance (GT) and glucose challenge test (GCT) ≥ 200 mg/dL. All of these factors probably represent the magnitude of the insulin resistance, which is the hallmark of future diabetes and of other vascular complications. Similarly, Bian et al.⁶⁷ reported a diagnosis of diabetes 1–5 years postpartum in 33.3% of patients with previous GDM ($n = 45$), but only 9.7% ($n = 31$) of those with IGT and 2.6% ($n = 39$) of normal controls. Two or more abnormal OGTT values during pregnancy, a blood glucose level exceeding the maximal values at 1 and 2 hours after oral glucose loading, and high pregnancy BMI were all useful predictors of diabetes in later life.

To determine if recurrent episodes of insulin resistance (i.e., another pregnancy) contribute to the decline in beta-cell function that leads to type 2 DM in high-risk individuals, Peters et al.⁶⁸ investigated 777 Latino women with a history of GDM. Among the 87 (13%) who completed an additional pregnancy, the rate ratio of type 2 DM increased to 3.34 (95% CI 1.80–6.19), compared with women without an additional pregnancy, after adjustment for other potential diabetes risk factors during the index pregnancy (antepartum oral glucose tolerance, high fasting glucose, gestational age at diagnosis of GDM) and during follow-up (postpartum BMI, glucose tolerance, weight change, breast-feeding, and months of contraceptive use). Weight gain was also independently associated with an increased risk of type 2 DM; the rate ratio was 1.95 (95% CI 1.63–2.33) for each 4.5 kg gained during follow-up after adjustment for the additional pregnancy and other potential risk factors. These data show that a single pregnancy, independent of the well-known effect of weight gain, accelerates the development of type 2 DM in women with a high prevalence of pancreatic beta-cell dysfunction.

What about milder, diet-controlled GDM? Damm⁶⁹ reported abnormal glucose tolerance in 34.4% of 241 women 2–11 years after a diabetic pregnancy (3.7% IDDM, 13.7%

type 2 DM, 17% IGT), in contrast to a control group in which none of the women had diabetes and 5.3% had IGT. The independent risk factors for later development of diabetes were fasting glucose levels at diagnosis of GDM, delivery >3 weeks before term and abnormal OGTT 2 months postpartum. Low insulin secretion at diagnosis of GDM was also an independent risk factor. Even the nonobese glucose-tolerant women with previous GDM had a metabolic profile of type 2 DM, i.e., insulin resistance and impaired insulin secretion. Thus, the first OGTT should probably be performed 2 months postpartum to identify the women who are already diabetic and the women who are at highest risk of later development of overt diabetes.⁶⁹ Interestingly, according to Fletcher et al.'s study, both women with a history of GDM and their children are at risk of progressing to type 2 DM.⁷⁰ Whether this effect is due to a genetic or an in utero influence has yet to be determined.

Overall a systematic review and meta-analysis of 20 studies that included 675,455 women and 10,859 type 2 DM events concluded that the RR for women who had GDM of developing subsequent type 2 DM compared with women who had a normoglycemic pregnancy was 7.43, 95% CI of 4.79–11.51.⁷¹

Summary

The IDF estimate that in 2013 diabetes affected 21.4 million live births, which is 16.8%, of which 16% were due to gestational diabetes. This is set in the context of the prediction that the total number of cases of diabetes will rise by 55% from 382 million in 2013 to 592 million in 2035.⁴ This should alert physicians to the need to direct special attention to this population, especially in developing countries.

The data presented in this chapter indicate that the epidemiology of GDM is characterized by several features:

- Differences in screening programs and diagnostic criteria have made it difficult to compare frequencies of GDM among various populations. Nevertheless, race has been proven to be an independent risk factor of GDM, which varies in prevalence in direct proportion to the prevalence of type 2 DM in a given population or ethnic group.
- Identifiable predisposing factors for GDM include high maternal age, multiparity, obesity, previous delivery of a macrosomic infant, and a family history of diabetes.
- In the absence of risk factors, the incidence of GDM is low. Therefore, some authors suggest that selective screening may be cost-effective, especially in view of the forecasted rise in the burden of GDM.
- PCOS is an important risk factor for GDM, with special similarity in the existence of insulin resistance.
- The genetic diathesis is not well understood.
- The recurrence rate of GDM (35%–80%) is influenced by parity, BMI, early diagnosis of GDM, insulin requirement, weight gain, and the interval between pregnancies.

- GDM carries a significantly increased risk of an adverse pregnancy outcomes relative to women with normal glucose tolerance.
- Women with an early diagnosis of GDM represent a high-risk subgroup, with an increased incidence of obstetric complication, recurrent GDM, and development of type 2 DM.
- Another subgroup of GDM is characterized by an increased risk of diabetic embryopathy, perhaps due to preexisting but undetected type 2 DM. This should be

considered in all patients with early diagnosis of GDM, accompanied by appropriate patient counseling.

- Hypertensive disorders in pregnancy and afterward is more prevalent in women with GDM. One possible mechanism is insulin resistance.
- Women with GDM are at increased risk of developing type 2 DM, especially obese patients, those who were diagnosed before 24 weeks gestation, and those who required insulin for glycemic control.

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9 Genetics of diabetic pregnancy

Komal Bajaj and Susan J. Gross

Introduction

Recent discoveries due to advances in molecular technology have underscored the important role genetic factors play in the development, treatment, and consequences of the diabetic pregnancy. This chapter reviews the genetic etiology of maternal diabetes, factors influencing pregnancy outcome, and what is known of the epigenetic consequences of hyperglycemia in pregnancy.

Gestational diabetes and relationship to type 1 and type 2 diabetes

Insulin resistance is a normal physiological alteration that occurs during pregnancy. Gestational diabetes mellitus (GDM) may develop when this normal resistance is coupled with pancreatic beta-cell insufficiency. Women diagnosed with GDM are at much higher risk of developing type 2 diabetes mellitus (T2DM) after pregnancy, ranging between 17% and 63% within 15 years, depending upon the population studied.¹ The connection between GDM and significantly increased risk of T2DM suggests that pregnancy serves as a stressor that often catalyzes progression to diabetes in predisposed individuals.²

GDM and T2DM share several common risk factors and underlying pathophysiology.³ Both conditions are associated with an elevated body mass index (BMI) and history of abnormal glucose tolerance. The hallmark of both conditions is a peripheral insulin resistance coupled with a relative insufficiency in pancreatic beta-cell insulin production. There are striking parallels between these two diseases, suggesting that there is considerable overlap between the genetic contributors to GDM and T2DM. Both are in fact strongly influenced by genetic and environmental factors. Table 9.1 highlights the relative role genetic factors and obesity play in early-onset T2DM, GDM, and late-onset T2DM.

Unlike GDM and T2DM, type 1 diabetes mellitus (T1DM) is characterized by autoimmune destruction of beta cells. T1DM is typically diagnosed well before reproduction.⁴ Table 9.2 outlines genes in which alterations are associated with susceptibility to T1DM, the majority of which relate to immunologic function. The remainder of this chapter will focus on heritable components of GDM, and, since they share similar pathophysiology, T2DM.

The foundation: Lessons learned in a pregenomic era

Prior to widespread use of advanced techniques such as next-generation sequencing and arrays, the contribution of genetic factors to a disease was often characterized by observations made through family history, the study of twins, analysis of general population databases, and the characterization of rare disorders known to run in families.

A patient's family history may provide clues as to conditions a patient is at risk for in her lifetime. The World Health Organization and the American College of Obstetrics and Gynecology both stress the importance of obtaining a thorough family history as part of a patient encounter.^{14,15} Family history alone serves as a predictor of GDM.¹⁶ When compared to individuals without any parental history of diabetes, those that reported even one parent with diabetes had a 2.3-fold risk of developing GDM. Furthermore, women with a diabetic sibling had an 8.4-fold increased risk of GDM.

Individuals who come from Hispanic, African, Native American, Asian, and Pacific Islander background are at increased risk for GDM.¹⁷ The prevalence of GDM in specific populations has been reported to be as high as 22%, whereas the prevalence in populations not considered to be high risk is between 2% and 5%.¹⁸ Such increased prevalence suggests a greater hereditary susceptibility in those populations.

Monogenic diabetes

While GDM is a multifactorial disorder, with a polygenic heritable and environmental component, there are monogenic forms of diabetes that comprise a small but important cohort of patients with diabetic pregnancy.

Maturity onset diabetes of the young

The term "maturity-onset diabetes of the young (MODY)" dates back to the 1960s when diabetes was classified into two forms—"juvenile onset" and "maturity onset." MODY is characterized by insulin-dependent diabetes diagnosed prior to age 25 without the presence of autoantibodies.¹⁹ MODY accounts for up to 5% of diabetes and is inherited in an autosomal dominant fashion. The clinical features of MODY are heterogeneous and in and of themselves may not

Table 9.1 Comparison of the relative role of genetic factors and obesity in young-onset type 2 diabetes, gestational diabetes, and late-onset type 2 diabetes

	Early-onset type 2 diabetes	Gestational diabetes	Late-onset type 2 diabetes
Age of diagnosis (years)	25–45	18–40	>45
Parental history of type 2 diabetes	+++	++	+
High prevalence racial origin	+++	++	+
Obesity	+++	+++	+

Source: Forbes, M. and Hattersley, A.T., The genetics of diabetic pregnancy, in: *Textbook of Diabetes and Pregnancy*, Hod M, Jovanovic LG, and Di Renzo GC (Eds.), 2007, pp. 466–474. With permission.

Table 9.2 Genes associated with type 1 diabetes

Gene(s)	Location
HLA class I and HLA class II genes	6p21.3
Insulin receptor (INS)	19p13.3
Cytotoxic T-lymphocyte-associated protein 4 (CTLA4)	2q33.2
Interleukin 2 receptor α (IL2R α)	10p15.1
Interferon induced with helicase C domain 1 (IFIH1)	2q24.2
C-type lectin domain family 16 (CLEC16A)	16p13.13
Th1 transcription factor (STAT4)	2q32.2-q32.3

Sources: Stankov, K. et al., *Pediatrics*, 132(6), 1112, 2013; C-type lectin domain family 16, available from: <http://omim.org/entry/611303>, accessed on April 29, 2014; INSR insulin receptor, available from: <http://www.ncbi.nlm.nih.gov/gene/3643>, accessed on April 29, 2014; Cytotoxic T lymphocyte-associated 4, available from: <http://omim.org/entry/123890>, accessed on April 29, 2014; Interleukin 2 receptor, alpha, available from: <http://omim.org/entry/147730>, accessed on April 29, 2014; Boucas, A.P. et al., *Arq. Bras. Endocrinol. Metabol.*, 57(9), 667, 2013; Knudsen, N.H. and Lee, C.H., *Diabetes*, 62(12), 4002, 2013; HGNC, Histocompatibility complex, available from: <http://www.genenames.org/genefamily/hla.php>, accessed on April 29, 2014.

raise suspicion for a monogenic syndrome unless a family history is clearly suggestive of an autosomal dominant pattern. This is further complicated by the fact that all types of MODY exhibit variable penetrance—not all individuals carrying a particular gene change will develop MODY.²⁰ Patients with MODY are typically diagnosed by age 25 and are often misclassified as having either T1DM or T2DM.²¹ A clearly distinguishing feature is the lack of autoantibodies. Patients with MODY are categorized into different types depending on the gene mutation. Table 9.3 highlights the gene defects associated with the various types of MODY.

Glucokinase (GCK) is an enzyme present in the β -cells of the pancreas that helps the cells, through phosphorylating glucose to glucose-6-phosphate, accurately detect circulating glucose and adjust insulin secretion accordingly. A loss of function mutation in the *GCK* gene impacts the ability to detect glucose at lower levels, thereby causing a rise in the homeostatic set point of blood glucose in that individual. Glucokinase monogenic diabetes (GCK-MODY) has been estimated to have a prevalence of 1.1 in 1000 primarily European population and that the prevalence in women with GDM is at least 0.9%.²⁷ Fifty percent of the fetuses of women with *GCK* mutations will inherit the mutation. It is expected that an unaffected fetus of a mother with a *GCK* mutation would produce excess insulin in response to the increased circulating maternal blood glucose, causing an increase in birth weight compared to a fetus with the

GCK mutation. In fact, a 700 g birth weight difference was seen between infants that did not carry the mutation and those that inherited the mutation from their mother.^{28,29} There are currently no standardized guidelines as to how to manage women with *GCK* mutations during pregnancy to minimize the risk of maternal and fetal complications.

While it is impractical to consider testing every woman with GDM for *GCK* mutations, narrow fasting glucose, BMI levels, and family history have been suggested as parameters that can be utilized to select patients with GDM for genetic testing.^{27,30} For example, using a BMI of <25 kg/m² and fasting glucose of ≥ 5.5 mmol/L during pregnancy as screening criteria, 2.7 women with GDM would need to be tested to find one case of *GCK*-MODY and 66% of all cases would be detected.²⁷

Mitochondrial mutations

The mitochondrial tRNA leucine 3243 mutation (3243 mtDNA) results in a rare form of maternally inherited diabetes and deafness. There is variable expressivity of the condition, though all cases have some level of aberrant insulin secretion and sensorineural deafness. The mean age of onset of symptoms is between 30 and 40 years of age. A proposed mechanism of disease is that diabetes develops due to an inappropriate storage of triacylglycerols, resulting in deterioration of pancreatic β -cell function.³¹ The mutation

Table 9.3 Types of maturity-onset diabetes of the young

Type	Gene defect	Physiologic defect	MODY cases
MODY 1	Hepatocyte nuclear factor-4- α	Loss of function mutation results in decreased insulin secretion in response to glucose	<10%
MODY 2	Glucokinase gene	Several different mutations result in faulty glucose detection	15%–30%
MODY 3	Hepatocyte nuclear factor-1- α	Aberrant insulin secretion and altered renal excretion of glucose	50%–60%
MODY 4	Insulin promoter factor 1 (PDX1)	Decreased activation of the insulin gene in response to hyperglycemia	Rare
MODY 5	Hepatocyte nuclear factor-1- β	Atrophy of the pancreas	5%–10%
MODY 6	Neurogenic differentiation factor-1	Pancreatic development	Rare
MODY 7	Kruppel-like factor 11	Transcription factor	Rare
MODY 8	Bile salt-dependent lipase (CEL)	Pancreatic function	Rare
MODY 9	PAX4	Differentiation of endocrine pancreas	Rare
MODY 10	Insulin gene (INS)	Aberrant insulin production	Rare
MODY 11	B-lymphocyte tyrosine kinase (BLK)	Modification of insulin transcription factors	Rare

Sources: Naylor, R. and Philipson, L.H., *Clin. Endocrinol.*, 75(4), 422, 2011; Shields, B.M. et al., *Diabetologia*, 53(12), 2504, 2010; Thanabalasingham, G. and Owen, K.R., *Br. Med. J.*, 343, d6044, 2011; Maturity-onset diabetes of the young, Type 7, available from: <http://omim.org/entry/610508>, accessed on April 23, 2014; Maturity-onset diabetes of the young, Type 8, available from: <http://omim.org/entry/609812>, accessed on April 23, 2014; Maturity-onset diabetes of the young, Type 10, available from: <http://www.genetests.org/disorders/?disid=315205>, accessed on April 23, 2014; Tyrosine kinase, B-lymphocyte specific, BLK, available from: <http://omim.org/entry/191305>, accessed on April 24, 2014.

has been well described in several different populations.^{32,33} Since the 3243mtDNA mutation leads to an insulin secretion defect, not a defect in insulin sensitivity, these patients initially do respond to medications that increase secretion such as glyburide. However, since there is a progressive loss of insulin secretion, the use of insulin is eventually required.

Technological advancements and definition of terms

Completed in 2003, the Human Genome Project produced a high-quality sequence of the human genome and provided details regarding its structure and organization. This was followed by the International HapMap Project in 2005, which provided a catalog of common genetic variants in human

beings and how they are distributed among diverse populations.³⁴ Both these important initiatives, along with advances in molecular technologies such as arrays and next-generation sequencing, provided the foundation for investigators to be able to evaluate many genes at one time and begin to make meaning of changes found in genotypes of many different individuals and populations. See further Table 9.4.

Genetic predisposition to gestational diabetes and type 2 diabetes in a genomic era

Though genome-wide association studies (GWAS) are not without their limitations, they have provided new insight into disease pathways and begun to dissect complex genetic

Table 9.4 Definitions of terms commonly utilized during the discussion of advanced molecular techniques

Term	Definition
Epigenetics	Any process that alters gene activity without changing the DNA sequence itself and leads to modifications that can be transmitted to daughter cell. ³⁵
Exome	Composed of all exons, which are the coding portions of genes. ³⁶
Genome	The entire genetic information (genes) for an organism, which is maintained in the nucleotide sequence of DNA; each organism has only one genome. ³⁷
Genome-wide association study	An approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. ³⁸
Locus (loci)	A specific location of a gene or DNA sequence.
Monogenic	A phenotype or disease that is the result of a change within a single gene.
Polygenic	The combined action of alleles of more than one gene contribute to a particular phenotype or disease. ³⁹
Single-nucleotide polymorphism	Often called SNPs, these are the most common type of genetic variant in any species. Each SNP represents a difference in one nucleotide. ⁴⁰

Table 9.5 Genes and locations associated with type 2 diabetes mellitus

Gene	Location
<i>KCNJ11</i>	11p15.1
<i>HHEX/IDE</i>	10q23.33
<i>SLC30A8</i>	8q24.11
<i>KCNQ1</i>	11p15.5-p15.4
<i>WFS1</i>	4p16.1

Sources: Saxena, R. et al., *Science*, 316(5829), 1331, 2007; Zeggini, E. et al., *Science*, 316(5829), 1336, 2007; Steinthorsdottir, V., *Nat. Genet.*, 39(6), 770, 2007; Scott, L.J. et al., *Science*, 316(5829), 1341, 2007; Williams, A.L. et al., *Nature*, 506(7486), 97, 2014; Unoki, H. et al., *Nat. Genet.*, 40(9), 1098, 2008; Sladek, R. et al., *Nature*, 445(7130), 881, 2007; Hayes, M.G. et al., *Diabetes*, 62(9), 3282, 2013.

architecture.⁴¹ GWAS and other forms of analysis allow for the discovery of variants associated with disease in genes not otherwise implicated in the disease process as well as the identification of variants outside coding regions of DNA. These insights provide important clues to the pathogenesis of common diseases, including new loci related to diabetes susceptibility.⁴² The following text summarizes some examples of genetic susceptibility categorized by suspected gene function. While this area of research is constantly growing and changing, the examples highlight the types of information that is being generated in the genomic era.

Insulin action and release

Single-nucleotide polymorphisms (SNPs) in the *TCF7L2* gene have been associated with a significantly higher risk of T2DM in several different populations.^{43,44} The *TCF7L2* gene, located on chromosome 10q25.3, is a transcription factor that acts through regulation of pro-glucagon gene expression.⁴⁵ When compared to noncarriers, the relative risk of T2DM was 1.45 for heterozygotes of the at-risk allele and 2.41 for homozygotes of the at-risk allele.⁴⁴ Individuals with impaired glucose tolerance and the *TCF7L2* gene variant were more likely to progress to diabetes over 3 years than those without the variant (HR 1.55, CI 1.2–2).⁴⁶ Analysis in GDM also suggested an increased risk of GDM in individuals with *TCF7L2* variant (OR 1.653, 95% CI 1.416–1.930).⁴⁷

ABCC8, located on 11p15.1, codes for a receptor on the pancreatic beta cell involved in insulin secretion. Several variants within this gene have been associated with an increased risk of GDM and/or T2DM.⁴⁸ In the Han Chinese population, for example, the C allele of the –3 T/C polymorphism in intron 24 and the A allele of the R1273R in exon 31 were strongly associated with an increased susceptibility to gestational DM.⁴⁹

Pancreatic beta-cell development and function

Some of the loci uncovered by GWAS and other applications of next-generation sequencing related to diabetes susceptibility are in genes involved in pancreatic development and

function (Table 9.5). The attributable risk of T2DM associated with the allelic variants within each of these genes has been studied in several diverse populations.

Two of these genes, *KCNQ1* and *WFS1*, are also associated with other genetic syndromes. The *KCNQ1* gene encodes for a subunit of a potassium channel (KvLQT1). Mutations in the *KCNQ1* gene have been implicated in long-QT syndrome, a group of disorders involving a characteristic cardiac arrhythmia. SNPs in *KCNQ1* have also been shown to confer an increased risk of GDM in several different populations.^{57,58}

WFS1 is a gene involved in beta-cell survival. Mutations in this gene cause Wolfram syndrome, the features of which include diabetes, optic atrophy, and deafness.⁵⁹

Impact of the abnormal glycemic environment on fetus

The impact of maternal hyperglycemia and short-term adverse perinatal outcomes, including fetal macrosomia, is well known.⁶⁰ Over the last decade, it has become clear that exposure to a diabetic milieu in utero is associated with impaired glucose tolerance and defective insulin secretory response in offspring during adulthood, independent of genetic predisposition to diabetes based on family history.⁶¹ When a fetus is female, in utero exposure increases her risk of developing GDM in her own pregnancies, thereby perpetuating the transgenerational effect of hyperglycemia and contributing to the increase in T2DM.⁶² Furthermore, intra-uterine hyperglycemia is also associated with an increased risk of obesity and cardiovascular diseases as an adult.⁶³

There is a great deal of evidence to suggest that abnormal nutrition while in utero (both fetal overnutrition and undernutrition) results in epigenetic changes to genes in important metabolic pathways. Both animal and human models reveal altered methylation patterns^{64,65} after aberrant nutritional status in utero. Coined “the fetal origins of adult disease,”⁶⁶ this concept of early programming has tremendous public health implications. Because the epigenome is vulnerable during early development, encouraging patients to avoid such exposures during the preconceptional and pregnant state may have tremendous impact on the prevention on adult diseases.⁶³

Future frontiers

Pharmacogenomics is an area that holds tremendous potential for impact in the care of GDM in the future. The ability to develop individualized regimens based on the patient's genetic makeup may improve treatment outcomes. For example, glyburide (a sulfonylurea that stimulates the pancreas to release more insulin) has been utilized to successfully manage hyperglycemia during pregnancy.⁶⁷ Women who fail to achieve glycemic control on glyburide must be transitioned to insulin. It has been demonstrated that the cytochrome P450 CYP2C9 is involved in the metabolism of many drugs, including glyburide.⁶⁸ The *CYP2C9* gene has several polymorphisms, and the degree of blood glucose reduction appears to differ depending upon the genotype.⁶⁹ Though further studies are needed, it is quite possible that in the future testing a patient's genetic makeup to help guide treatment regimens may be a regular part of the care of the gestational diabetes.

Inflammatory markers have been associated with the development of diabetes.⁷⁰ Abnormal metabolic disturbances at the level of the adipocyte have been observed in women with GDM.⁷¹ Aberrant levels of galectin-1, a carbohydrate binding protein, in the second and third trimester are associated with GDM.⁷² Modern “omics” approaches—genomics, metabolomics, proteomics, and transcriptomics—attempt to characterize patterns of various biological markers and translate those patterns into deeper insights regarding normal function and disease processes. The creation of a metabolic “fingerprint” for GDM, for example, would allow for deciphering biological processes, which translates into opportunities for prevention, early diagnosis, and treatment of disease.⁷³

The “exposome,” like modern “omics,” attempts to characterize patterns in order to gain insight into disease. In this case, the “exposome” includes all the exposures an individual encounters from conception onward. Efforts to implement assessment tools to measure early-life exposures and their impact on health outcomes are underway and may shed light on the development and outcome of the diabetic pregnancy.⁷⁴

Practice points

- Monogenic forms of diabetes comprise a small but important cohort of patients with diabetic pregnancy.
- Advances in molecular technology and understanding of the human genome have contributed to the identification of new loci and pathways associated with increased susceptibility to diabetes.
- Exposure to a diabetic environment in utero increases the risk of adult-onset chronic diseases such as obesity and diabetes.

Research agenda

- Deconstruct the genetic basis of the complicated metabolic pathways leading to diabetes in pregnancy.
- Further characterize the epigenetic changes related to exposure to a hyperglycemic environment and their impact on adult-onset diseases.
- Establish individualized treatment regimens based on genetic variants and metabolic profile.

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10 Animal models in diabetes and pregnancy research

Catherine Yzydorczyk, Delphine Mitanchez, and Umberto Simeoni

Maternal diabetes constitutes an unfavorable environment for the development of the fetus. The concept that exposure in utero to a hyperglycemic environment has both a short- and a long-term impact in the offspring is notably demonstrated by animal studies. Animal models for diabetes and pregnancy offer various ranges of hyperglycemia, which can lead to fetal organ alterations, congenital malformations, and micro- or macrosomic fetuses and affect the offspring later in life. The purpose of this review is to give a comprehensive view of the most frequently studied animal models of diabetes and to demonstrate how animal models have permitted to elucidate some mechanisms involved in the pathogenesis of diabetes.

Animal models

Animal models of pregestational type 1 diabetes

Type 1 diabetes (T1D) in humans is characterized by a specific destruction of the pancreatic beta cells, commonly associated with immune-mediated damage.¹

Surgical models

In rodents, after puberty, partial pancreatectomy (removal of 95% of pancreatic weight) leads to a decrease in the number of beta cells and therefore to uterine and placental defects and altered fetal glucose metabolism regulation, associated with mild maternal diabetes (glycemia between 150 and 200 mg/dL). Insulin administration is not required and pregnancy rates are usually good. However, postsurgery mortality is relatively elevated (20%) and a delay (2–3 months) exists between the surgical procedure and the development of diabetic symptoms.²

Chemical model

In general, human T1D is reproduced by streptozotocin (STZ) administration to rodents during adult life.³ STZ is a nitrosourea derivative isolated from *Streptomyces achromogenes*.⁴ It is a powerful alkylating agent that has been shown to interfere with glucose transport⁵ and glucokinase function⁶ and able to methylate DNA. Nevertheless, it is generally accepted that the cytotoxicity produced by STZ depends on DNA alkylation.⁷ STZ, relatively similar to glucose, is

transported inside the cell only by the glucose transporter-2 (GLUT-2) (STZ is not recognized by the other GLUTs). Beta cells of the islets of Langerhans express high levels of GLUT-2, therefore making them more vulnerable to STZ toxicity.⁸

Various modes of injection (intravenous or intraperitoneal) and different doses (30–50 mg/kg) have been proposed. Also, STZ administration can be performed during the pregestational or gestational period that leads to the development of severe or mild diabetes associated with two opposite fetus phenotypes, intrauterine growth restriction (IUGR), or macrosomia. In the case of mild diabetes, mothers are hyperglycemic (with blood glucose concentrations comprised between 120 and 300 mg/dL) and hypoinsulinemic and deliver macrosomic fetuses, whereas in the case of severe diabetes, mothers are insulin deficient and hyperglycemic. This leads to small-for-gestational-age fetuses, characterizing IUGR, and to fetuses with congenital malformations.⁹

Spontaneous animal models

The nonobese diabetic (NOD) mice and biobreeding (BB) rats develop spontaneous pregestational T1D.

NOD mice develop a mild form of diabetes characterized by macrosomic fetuses and adiposity. Pancreatic beta cells become infiltrated by mononuclear cells that lead to the development of insulinitis (inflammation of the islets of Langerhans, present in NOD mice at 4–5 weeks old), followed by beta cell destruction, and a decrease in circulating insulin concentrations. Mild diabetes is present between 12 and 30 weeks of age. However, insulin-dependent diabetes develops spontaneously only in 9% of NOD at 12 weeks of age and in 80% of them at 30 weeks of age and is more prevalent in females.¹⁰ Contrary to human T1D, ketoacidosis is relatively mild and affected animals can survive for several weeks without insulin injection.

BB rats, which were originally derived from a Canadian colony of outbred Wistar rats, are a good model for the study of perinatal morbidity, small-for-gestational-age fetuses, and malformations.

Weight loss, polyuria, polydipsia, hyperglycemia, and insulinopenia appear around 12 weeks of age. Also, ketoacidosis is severe and can be fatal if exogenous insulin is not administered. The incidence is similar in males and females.^{11,12}

Animal models of type 2 diabetes

Type 2 diabetes (T2D) represents a heterogeneous group of disorders, which is characterized by insulin resistance (IR) and impaired insulin secretion, and defined by a raise in fasting or postload blood glucose concentration.

Spontaneously diabetic rats

The Goto-Kakizaki (GK) rat model is a model of nonobese T2D.^{13,14} This strain was developed by the successive inbreeding of Wistar rats with the administration of highest blood glucose concentrations.¹⁵ GK rats develop some features that can be compared with the complications of diabetes observed in humans, as renal lesions,¹⁶ structural changes in peripheral nerves,¹⁷ and abnormalities of the retina.¹⁸ GK offspring exposed throughout gestation to mild diabetes presents a severe reduction in beta cell mass. This is associated with a lack of pancreatic reactivity to glucose that seems to be the consequence of a reduction in cell proliferation, a defect of insulin-like growth factor signaling pathways, and an increased apoptosis in the fetal pancreas.^{19,20}

Chemical model

Human T2D is reproduced in rodents by administration of different doses of STZ (80–100 mg/kg) in the neonatal period.²¹ The timing of the neonatal STZ injection seems to be important in determining degrees of severity of the subsequent diabetic state. It has been shown that the effects observed in adulthood were higher if STZ was administrated 5 days after birth²² compared to an administration on the day of birth.²³ STZ administrated 5 days after birth leads in adulthood to the development of a frank basal hyperglycemia and glucose intolerance, an increase in glycosylated hemoglobin, a strong decrease in the pancreatic insulin stores, a reduction (50%) of basal plasma insulin level, and a default of plasma insulin response to glucose *in vivo*.²⁴ Variations in the effects according to the timing of STZ administration could be explained by the recovery of pancreatic insulin stores due to the regeneration of part of the beta cells after the STZ insult.²⁵

Animal model of gestational diabetes

The heterozygous leptin receptor-deficient (Lepr(db/+)) mouse shows an autosomal recessive mutation in the leptin receptor gene and serves as an animal model with gestational diabetes mellitus (GDM). During gestation, compared to wild-type, db/+ dams present hyperphagia, hyperleptinemia, greater weight gain, abnormal insulin and glucose tolerance tests and their offsprings are heavier at birth.²⁶

Outcomes in animal offspring of maternal diabetes exposure

Congenital malformations

Maternal diabetes affects embryonic development and induces congenital malformations. Skeletal, facial, cardiac, and visceral malformations have been observed in the

fetuses at late gestation in a rat model with STZ-induced diabetes.^{27,28} Congenital malformations are also mentioned in fetuses from other models of diabetes such as the GK rats²⁹ and the BB rats with T1D.³⁰ In NOD model, principally, neural tube defects and skeletal alterations have been observed in embryos from NOD female with overt diabetes.³¹

Also, congenital anomalies could be the result of a default in gene expression involved in the control of the developmental processes. A decrease in Pax-3 (a gene that encodes a transcription factor necessary for neural tube closure) expression has been involved in neural tube and cardiac malformations observed in mice with STZ-induced diabetes.^{32,33}

Fetal organ alterations and long-term outcomes

Maternal diabetes is also associated in the offspring with an alteration in the development of many organs. Notably, the heart, kidney, liver, and endocrine pancreas are the most affected, and cardiometabolic diseases may develop later in life.

Cardiovascular and renal systems

The heart of fetuses from rats with STZ-induced diabetes is hypertrophic, while the offspring born from rats with severe maternal diabetes shows cardiovascular dysfunction. In early adulthood, a decreased heart rate, an impairment of the vascular function characterized by a reduction of endothelium-dependent vasodilatation capacity to acetylcholine, and an increase in vasoconstriction to noradrenaline have been shown in the offspring exposed to diabetes *in utero*,^{34,35} therefore predisposing to cardiovascular diseases. Fetuses from rats with STZ-induced diabetes show nephrogenesis characterized by a decrease in kidney weight and nephron number,³⁶ which leads in adulthood to hypertension^{37,38} and renal dysfunction.³⁹

Liver

The fetal and neonatal livers from STZ-induced diabetic dams show an increase in lipid accumulation. A decrease in insulin receptors has been observed in the fetal liver of diabetic rats.⁴⁰ Alterations in signaling pathways have also been evidenced. In female offspring (db/+), higher hepatic glucose-6 phosphatase activity has been found to be associated with a decrease of Akt phosphorylation that leads to the development of an IR in the liver at adulthood.²⁶ Maternal diabetes interferes with fetal hepatocyte proliferation and differentiation. It leads to hepatic damage characterized by the formation of edematous blood vessels, karyolytic and pyknotic hepatocyte nuclei, and distortion of blood sinusoids. Also, mitochondrial damage in fetal hepatocytes was observed with an increase in apoptotic cells⁴¹ that can participate in enhancing the liberation of reactive oxygen species (ROS) and so contribute to the oxidative stress (OS). High levels of lipid peroxidation (thiobarbituric acid measurement) have been observed in the fetal liver of diabetic pregnant rats associated with a decrease in vitamin E levels that can be associated with congenital malformations.⁴²

Pancreas

The fetal beta cells are extremely sensitive to maternal diabetes. In mothers with mild hyperglycemia, rat fetuses present hypertrophy of the endocrine pancreas, hyperplasia of beta cells, and an increase of pancreatic and plasma insulin concentrations. A positive correlation has been observed between maternal glycemia and fetal weight.^{43–45}

In the case of severe maternal diabetes, fetal beta cell mass has been shown to be either reduced or increased. A reduction of beta cell mass decreases the capacity of insulin secretion, whereas an enhancement of beta cell mass increases the capacity of insulin secretion.^{46,47} When the fetus is exposed to very high concentrations of glucose, it will develop islet hypertrophy and beta cell hyperactivity associated with early hyperinsulinemia. On the other hand, the number of beta cells is decreased, and they are disorganized and depleted in insulin granules; therefore, they are not able to secrete insulin *in vivo* and *in vitro*.⁴³ This results to hypoinsulinemia, a decrease in fetal glucose intakes.⁴⁸ A negative correlation has been mentioned between maternal glycemia and fetal weight. Long-term outcomes involve an increase of obesity rate, an impairment of glucose tolerance, and an increased risk of IR, contributing to the development of T2D in adulthood.⁴⁵

Animal models of diabetes: The role of intrauterine environment

An alteration of fetal environment may program the development of metabolic diseases later in life.

Nutrition alteration

Maternal nutrition represents a major factor, and it is now well recognized that inappropriate nutrition *in utero* has notable metabolic consequences in adulthood.⁴⁹ Beta cell development is irreversibly damaged by inadequate nutrition during critical periods of fetal development.⁵⁰

Caloric-nutrient restriction

In rat, global restrictions (40%–50% of normal intake) during the last week of gestation lead to low birth weight (LBW) in offspring and a decrease in beta cell mass that persists in adulthood with a reduction in insulin content.^{51,52} Also, nutrient restriction during the suckling period leads to a permanent reduction in beta cell mass in offspring and the development of glucose intolerance with aging.⁵³

Protein restriction

In pregnant rats fed with a low-protein (LP) diet, the maternal plasma glucose and insulin levels are normal and fetuses are normoglycemic. Nevertheless, the development of the fetal endocrine pancreas is impaired, which leads to a deficient insulin response and to fetal growth restriction. The offspring from LP dams presents a deficit in beta cell mass,⁵⁴ reduced pancreatic insulin content and islet size, altered

islet cell proliferation, decreased islet vascularization,⁵⁴ and increased islet cell apoptosis.⁵⁵ In basal condition, they are normoglycemic, but glucose tolerance is impaired and insulin-stimulated glucose uptake is reduced^{54,56,57} in the muscle, adipocytes, and liver.⁵⁸ There is also a gender effect: The male offspring undergo an impairment in glucose tolerance (17 months of age) and, thereafter, develop T2D and IR,⁵⁹ whereas female offspring only develop hyperinsulinemia and impaired glucose tolerance in a more advanced age (21 months).⁶⁰

High-fat diet

In rats, maternal high-fat (HF) diet intakes during gestation lead to the development of some features of the metabolic syndrome (MS) in male offspring characterized by increased body weight, plasma levels of insulin, glucose, free fatty acids, and fatty acids and also glucose intolerance.^{61,62} Furthermore, in female offspring, paternal HF diet exposure leads to an early impaired insulin secretion and glucose tolerance that worsened with advanced age.⁶³

Uteroplacental insufficiency

Uteroplacental insufficiency is the major cause of IUGR. In rat models, IUGR can be induced by maternal bilateral uterine artery ligation during late gestation (on day 19 of gestation). Their pups have LBW and decreased levels of glucose, insulin, and insulin-like growth factor-1. Thereafter, diabetes appears in adulthood at approximately 16–26 weeks of age associated with a default in beta cell secretory capacity and IR.⁶⁴

Mechanisms

Oxidative stress

Diabetic pregnancy and macrosomia are associated with increased OS. Protein glycation and glucose auto-oxidation may generate ROS and therefore catalyzed lipid peroxidation.⁶⁵ ROS can be detoxified by endogenous antioxidant enzymes (superoxide dismutase [SOD], catalase, glutathione peroxidase, and reductase) and vitamins (A, E, and C).

An increase in OS and an impairment of antioxidant enzymes have been found in fetuses and neonates from rodent experimental models with mild and severe STZ-induced diabetes.^{66,67} In offspring with advanced age, maternal protein restriction leads to an increase in OS levels, characterized by an increased lipid peroxidation (hexanoyl lysine adducts), decreased antioxidant defenses (SOD), and an increase in islet fibrosis markers (collagen I and III), which can lead to progressive beta cell loss and dysfunction.⁶⁸ A poor maternal nutrition leading to LBW followed by accelerated postnatal growth is associated with impaired antioxidant defenses (SOD expressions) and increased markers of senescence (p21 and p16) in the beta cells of pancreatic islets.⁶⁹ To confirm the role of OS in these metabolic alterations, nutritional and antioxidant therapies have been tested. Folic acid and antioxidant supplementations (α -tocopherol and ascorbate)

have been observed to decrease congenital malformations in term fetuses of rodents with STZ-induced diabetes.^{70,71} Also, omega-3 fatty acid consumption restores the antioxidant status of diabetic pregnant rats and decreases the rate of macrosomic pups at birth and lipid peroxidation (plasma thiobarbituric acid–reactive substance measurement) in diabetic mothers and their offspring.⁷²

Telomere shortening

Telomeres are repeated sequences of DNA (TTAGGG)_n at the end of chromosomes that protect them against inappropriate DNA fusion, breaks, and shortening into coding DNA sequences.⁷³ Thus, they are essential for chromosome stability. Telomeres have a high content in guanine and therefore are particularly susceptible to damage by OS,⁷⁴ and a positive correlation has been observed between OS and telomere shortening.⁷⁵ With each cycle of replication, the telomeres shorten; however, the telomerase makes additional copies of the hexanucleotide repeats to protect against this telomere loss. Data suggest that short telomeres may lead to premature beta cell senescence associated with a decreased beta cell mass and a defect in insulin secretion and glucose tolerance. Using a mice model deficient in telomerase, Kuhlow et al. have suggested that this enzyme is important to maintain glucose homeostasis.⁷⁶ In rat offspring, an LP diet exposure in utero followed by an accelerated postnatal growth leads to a higher number of short telomeres and fewer long telomeres in pancreatic islets, reflecting an accelerated islet telomere shortening.⁶⁹

Epigenetic regulation

Epigenetic modifications can be defined as changes in the pattern of gene expression without involving changes in the DNA sequence. The fetal environment can alter the epigenome in the offspring, therefore leading to different phenotypes.^{77–79} Three main pathways can silence, activate, or regulate the level and time of expression of many genes: DNA methylation, histone modifications (acetylation, methylation, ubiquitination, phosphorylation, or ADP ribosylation), and small noncoding RNAs, such as microRNAs (miRNAs).^{80,81} In general, these three epigenetic mechanisms appear to work together to regulate gene expression. DNA methylation or histone modifications can alter the expression of miRNAs, which can in turn regulate the expression level of DNA methyltransferases, histone methyltransferases, histone deacetylases, and methyl CpG-binding proteins and therefore regulate the epigenetic processes of DNA methylation and histone modifications.⁸⁰ Nowadays, it is relatively well established that epigenetic alteration/modification can affect several processes involved in glucose regulation and insulin secretion that can lead to the development of T2D.

DNA methylation

It is the best-known pathway. It usually leads to repression of transcription of the involved gene. Methylation takes place on CpG islands mainly located in the promoter region of

the genes. Usually, if these islands of the promoter region are unmethylated, the gene is transcribed, but when a significant part of the CpG islands is methylated, the gene can no longer be transcribed and is silenced. In early life, DNA methylation can be altered by many nutritional factors such as folate, choline, betaine, methionine, and vitamins B2, B6, and B12 (methyl donors).⁸² DNA methylation pattern can also be affected by OS. The replacement of guanine by the ROS radical adduct-8-hydroxyguanine affects the methylation of adjacent cytosine.⁸³ Therefore, this DNA modification can affect the development and thus increase the risk of developing cardiometabolic diseases later in life. A global DNA hypomethylation has been observed in the liver of rats with T1D.⁸⁴

LP diet is associated with impaired fetal growth and development of cardiometabolic diseases in the offspring. Many epigenetic changes have been reported in offspring exposed to a maternal LP diet. Hypomethylation of the promoter of the glucocorticoids receptor (GR) associated with a decrease in DNA methyltransferase-1 expression and in expression and binding of methyl CpG-binding protein-2 in the liver results in increased GR promoter activity and so can lead to the development of hypertension thereafter. An increased activation of the peroxisomal proliferator-activated receptor- α promoter has also been observed in the liver of these adult offspring exposed to maternal LP diet,⁸⁵ which can be associated with induction of dyslipidemia.⁸⁶

LP intakes during gestation in mice lead to DNA hypomethylation of the leptin promoter in adipose tissues associated with an alteration in body composition and increased food intakes in male offspring and so could contribute to the development of MS.⁸⁷

Histone modifications

In the nucleus of eukaryotic cells, DNA is coiled around octamers of globular proteins called histones, forming dense blocks of DNA and proteins named nucleosomes and that in conjunction form chromatin, the condensed form of DNA. Histones can be modified on the tails by methylation, acetylation, phosphorylation, biotinylation, ubiquitination, and ADP-ribosylation.^{79,80} These modifications facilitate or obstruct the access of DNA to transcriptional factors and, together with the other epigenetic factors, regulate gene expression.

In a rodent model of IUGR that expressed a lower level of Pdx1 (a transcription factor critical for beta cell function),⁸⁸ epigenetic modifications characterized by the loss of upstream stimulatory factor-1 binding at proximal promoter of Pdx1, recruitment of histone deacetylase 1 and the corepressor Sin3A, and deacetylation of histone H3 and H4 were observed. This resulted in Pdx1 silencing, which persisted from 2 weeks to 4 months of age and was responsible for the prediabetic state in rats.⁸⁹

Histone modifications were also proposed to decrease the expression of GLUT-4 (glycoprotein that facilitates glucose transport that is involved in the development of glucose intolerance) in the IUGR offspring. A reduction of glucose transport in the muscle is a feature of IR. Such alterations

persist at adulthood and could be an adaptive response to the decrease of insulin pancreatic production.⁹⁰

Also, histone modification and DNA methylation can be dependent on one another. Methylation of lysine 9 on H3 can promote DNA methylation, and in turn, CpG methylation can influence methylation of lysine 9 on H3.⁹¹

Noncoding RNAs

miRNAs are small single-stranded RNAs that do not encode proteins. Each miRNA binds to specific messenger RNAs (mRNAs) resulting in the degradation of target mRNA or inhibition of its translation into protein. miRNAs regulate the posttranscriptional expression level of many genes and processes such as apoptosis, cell growth, and differentiation in a large range of tissues. Therefore, miRNAs are involved in many processes including angiogenesis, cardiogenesis, nephrogenesis, and related diseases.⁹² miRNAs are critical regulators of metabolism. It has been shown that miR-103, miR-107, and miR-33 regulated insulin sensitivity and glucose homeostasis.^{93–95} Also, an overexpression of miR-143 was involved in the default of insulin pathway and glucose homeostasis.⁹⁶

Conclusion

The impact of an early exposure to an altered fetal environment (hyperglycemia, inadequate maternal nutrition) on the offspring's health and on the development of cardio-metabolic diseases in adulthood is robustly demonstrated in animal models. These models also can offer a major contribution in the understanding of the mechanisms leading to such alterations. However, they have some limits in mimicking human diseases.

An ideal animal model to mimic human T1D and T2D is not easy to develop. For T1D, this ideal animal model should be associated with an autoimmune destruction of beta cells at a very early stage of life to reproduce the human situation. However, in surgical animal models of diabetes, the decrease of beta cell number is the result of pancreatectomy, whereas in STZ-induced diabetes, beta cells are destroyed due to specific beta cell-induced death. The spontaneous animal models (NOD mice and BB rats) seem to be good models because the destruction of beta cells is the result of an autoimmune process. In BB rat models, diabetes develops around puberty, whereas this occurs in aged animals in NOD mice.

The ideal animal model of T2D should be a model with an IR and a default in pancreatic response resulting from

this IR. However, in the model with STZ-induced diabetes, the main alteration is the beta cell destruction.

In an optimal experimental model of GDM, levels of glycemia before gestation would be normal, and then, after midgestation, glucose intolerance and impaired insulin secretion would be observed with a perturbation in glucose and IR in the dams and therefore affect the fetus.

A satisfying model of GDM is db/+ mice in which diabetes occurs during gestation, but the deficiency in leptin receptor leads to phenotypes that differ from human GDM. In STZ-induced diabetes, the destruction of beta cells during pregnancy leads to a diabetic experimental model during the pregnant state.

Nevertheless, in all cases, the elevated glucose and other metabolic substrates in the maternal compartment reach the fetuses and are involved in the induction of short- and long-term outcomes of diabetes.

An alternative to the limits mentioned on rodent animal models with diabetes will be the use of larger animals that seem better to mimic the human diabetes.

Treatment of rabbit with alloxan is associated with the induction of T1D, notably on the long term. Injection of a monodose of alloxan (100 mg/kg) is rapidly taken up by the beta cells, which leads to the formation of free radicals and the fragmentation of beta cell DNA, as a consequence of the poor antioxidant defenses from these cells. Hypoinsulinemia and hyperglycemia have been observed 48 hours after the destruction of pancreatic b-cells.⁹⁷

In cats, some similar characteristics to T2D in human are reported. Cats develop T2D in middle age, associated with obesity, IR, and subsequent beta cell loss.⁹⁸

Administration of an HF diet and different doses of STZ in dog lead to features similar to human T2D, characterized by obesity, IR, and compensatory hyperinsulinemia followed by a decrease in pancreatic function.⁹⁹

The nonhuman primates (NHPs) present disease with many similarities with the human ones like obesity, IR, dyslipidemia, and hypertension. Likewise, NHP spontaneously develop T2D with advanced age and also when a hypercaloric diet is administrated.¹⁰⁰

Larger animal models of diabetes share important metabolic similarities with human pathology compared to rodent models. The life span to reproduce the natural history T2D and permit to study the long-term clinical complications observed in human. Moreover, larger animal models provide a valuable resource to test the safety and efficacy of therapeutic intervention prior to clinical trials.

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11 Pathologic abnormalities of placental structure and function in diabetes

Rhonda Bentley-Lewis, Maria Rosaria Raspollini, and Drucilla Roberts

Introduction

In 1892, Ballantyne wrote: “A diseased foetus without his placenta is an imperfect specimen, and a description of a foetal malady, unless accompanied by a notice of the placental condition, is incomplete. Deductions drawn from such a case cannot be considered as conclusive, for in the missing placenta or cord may have existed the cause of the disease and death. During intrauterine life the foetus, the membranes, the cord and the placenta form an organic whole, and disease of any part must react upon and affect the others.”¹ Indeed, a careful examination of the placenta contributes to the determination of the causes underlying fetal growth abnormalities, demise, or neonatal conditions. The correlation between placental histopathology and clinical data may augment our understanding of the sequence of pathologic events and enhance the management of the neonate or future pregnancies.

Although placental specimens are not routinely sent for pathological examination, there has been growing recognition of its importance.² Indications for placental referral include fetal conditions requiring admission to the neonatal intensive care unit and maternal diseases or disorders related to pregnancy, such as maternal diabetes.³ At a minimum, the placenta requires gross examination after delivery to identify any visible pathology. This macroscopic analysis should include assessment of the length and insertion site of the umbilical cord, the number of cord vessels, the state and color of the fetal surface and fetal membranes, the presence of abnormalities on the maternal surface, the color and the consistency of the villous tissue, and the presence of chorionic plate lesions. Any abnormal findings should prompt a complete pathologic examination regardless of clinical history.⁴

At term, the normal human placenta is a focal, disk-like thickening of the membranous sac that is achieved by splitting the membranes into two separate sheets, the chorionic plate and the basal plate. Both sheets enclose the

intervillous space as a cover and bottom. The intervillous space is perfused with maternal blood, which circulates freely and directly around the trophoblastic surface of the placental villi. The villi originate from a complex, treelike projection of the chorionic plate into the intervillous space (Figure 11.1). The villous surface is surrounded by the trophoblast and a core composed of stroma that supports the fetal vessels connected to the fetal circulation system via the chorionic plate and umbilical cord. At the placental margin, the intervillous space is obliterated as the chorionic and basal plates fuse together to form the chorion laeve.⁵

Pathophysiology of placental derangements in diabetes

Maternal diabetes mellitus complicates pregnancy through a variety of growth-promoting and growth-restricting forces that disrupt the normal development of both the fetus and placenta. Diabetes leads to increased inflammation, which inhibits implantation, similar to the effect of intrauterine contraceptive devices that induce local inflammation.⁶ In addition to inflammation, oxidative stress resulting from diabetes negatively impacts uteroplacental vascular function, thereby altering the maternal intrauterine environment. Because the placenta serves as the sole source of fetal oxygen and nutrients, metabolic derangement in the placental environment, such as changes in glucose and insulin levels, can affect fetal development.

Maternal glucose reaches fetal circulation freely; therefore, when there is maternal hyperglycemia, the ensuing fetal hyperglycemia has several possible effects on the developing conceptus. These adverse sequelae include hyperplasia of the islets of Langerhans, increased insulin stored in the islets, and a greater probability of single umbilical artery formation.⁷ Several studies have shown that additional placental findings in cases of maternal diabetes may be influenced by the level of dysglycemia or type of diabetes, possibly due

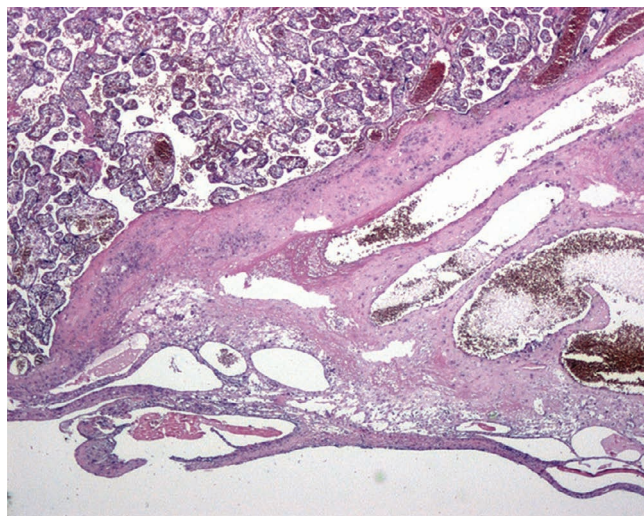


Figure 11.1 Hematoxylin-eosin section of normal placenta at term showing villi that form a complex treelike projection of the chorionic plate into the intervillous space.

to the different stages during pregnancy when the placenta is exposed to hyperglycemia.^{2,8–11} Maternal glycemic status can also influence the up- or down-regulation of insulin receptors on trophoblasts.¹² Because insulin does not physically cross the placenta into fetal circulation, the effect of insulin on maternal diabetes is indirect.

Insulin has also been shown to modulate ovarian steroidogenesis¹³ that, at the earliest stages of pregnancy, allows the development of normal endometrial receptivity.¹⁴ During the course of pregnancy, nondiabetic women experience a progressive decline in insulin sensitivity associated with hyperinsulinemia,¹⁵ a physiologic state required to preferentially direct maternal nutrients toward the fetoplacental unit.¹⁶ However, women with gestational diabetes mellitus have been shown to express abnormal insulin secretion¹⁷ and pronounced insulin resistance.¹⁸ The resulting protein kinase C (PK-C) activation and increased oxidative stress lead to endothelial dysfunction of the decidual capillary network. This dysfunction is associated with decreased vasodilation, increased leukocyte-endothelial cell adhesion, and increased vascular permeability.^{19,20}

Type 1 diabetes during pregnancy is also associated with dysregulation of glucose and oxygen metabolic pathways, both of which affect placental villous growth and function. Different degrees of changes in the syncytiotrophoblast, cytotrophoblast, trophoblastic basement membrane, and fetal vessels have been described and attributed to glycemic status. Alteration of placental development may contribute to increased risk of pregnancy complications such as preeclampsia, macrosomia, fetal growth restriction, and fetal hypoxia. However, the extent to which maternal glycemic control contributes to placental abnormalities is still being considered in detail²¹ additionally, several studies have identified histopathological placental abnormalities among women with well-controlled pregestational^{11,22–24} and gestational diabetes.^{25–27}

The fetal-placental vasculature, developed in the second week of pregnancy, is also negatively affected by maternal diabetes. Under normoglycemic conditions, the gestational sac invades the maternal decidua allowing the media and elastica of the uterine spiral arteries to loosen. The endothelium is then supported by connective tissue fibers. However, during diabetes in pregnancy, increased oxidative stress and the activation of protein kinase pathways, particularly PK-C and mitogen-activated PK, may impair placental vasculature formation. In addition, the response of the fetal-placental vasculature to vasoconstrictor and vasodilator agents in diabetic placentas is significantly attenuated compared to that of nondiabetic placentas.^{16,28} Consequently, the diabetic placenta may not be able to respond adequately to demands for altered blood flow, thereby leading to fetal compromise.²⁸

Gross examination

A recent comprehensive systematic review of the literature provides a critical examination of the gross and histopathological findings associated with dysglycemia in pregnancy.²¹ On initial gross examination, placental anomalies indicative of chronic insult may be present, including abnormal placental size and shape, infarcts or hemorrhages, cord defects, and membrane anomalies. While human placentas are generally round or oval, other shapes are not uncommon. Shape anomalies, such as a multilobulated placenta, may develop from abnormalities in fetal gene expression or fetal-maternal interactions. An abnormal maternal environment, such as the presence of submucosal leiomyomas or a uterine scar, unprotected membranous fetal vessels as seen in vasa previa, or early uteroplacental vascular compromise, can also alter the shape of the placenta.⁵

Placental weight, measured after removing the cord, membranes, and maternal blood clots, is a function of gestational age, fetal weight, and fetal gender. The placenta weighs approximately 450–550 g at term, and the fetal/placental weight ratio should be approximately 6–7. In pregnancies with appropriate-for-gestational-age infants, histological differences between diabetic and nondiabetic placentas are the most pronounced.²⁹ Placental weight heavier than the 95th or less than the 5th percentile for gestational age is often a sign of chronic insult. Maternal diabetes is often associated with large placentas heavier than the 90th percentile although the differential diagnosis also includes fetal hydrops, congenital syphilis, villous edema, and Beckwith-Wiedemann syndrome.³⁰

Cord length is usually between 40 and 70 cm with a diameter between 1 and 3 cm at term. A short or excessively long cord is related to an increased risk for fetal damage. Marginal cord insertion or velamentous cord insertion, which may be secondary to aberrant blastocyst implantation, may be associated with fetal or neonatal injury. Macroscopic analysis of cord vessels can reveal histopathologic features such as thrombosis of vessels or the presence of a single artery,

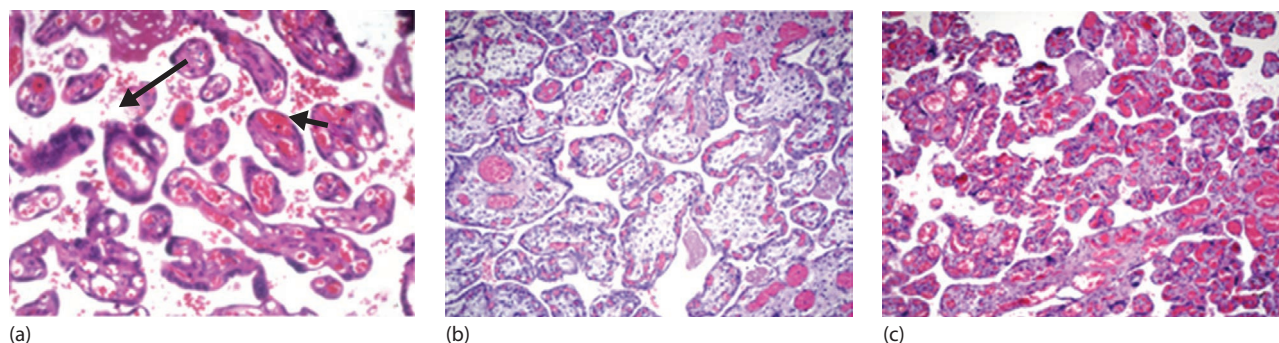


Figure 11.2 Section of a normal placenta at 38 weeks gestational age (a), a placenta at 38 weeks gestational age complicated by maternal insulin-dependent diabetes mellitus and chronic hypertension (b and c) (hematoxylin–eosin). In (b) the villi are widely separated due to premature branching, and the villi have fewer capillaries and larger and more numerous syncytial knots (arrow and arrowhead). (c) Shows a chronic abruption with the retroplacental hematoma (arrow) with an indented and infarcted parenchyma.

manifestations of vascular pathology, fetal malformation, or maternal diabetes.

The placental surface is red and spongy at term. A dark-red color suggests congestion of capillaries or chorangiosis that may be associated with maternal diabetes (Figure 11.2). Placental thickness is usually between 1.5 and 3 cm but diabetic placentas are often thicker. Macroscopic analysis of the fetal surface of the chorionic plate should include evaluation of the chorionic vessels for evidence of thrombosis. Dilated and/or discolored vessels suggest fresh thrombosis, while tan–white or yellow fibrosed vessels are indicative of an old thrombus. Thrombosis of chorionic vessels is more common in maternal diabetes but can also be seen in vascular anomalies accompanied by local trauma or stasis, including true knots of the umbilical cord, velamentous cord insertion, and umbilical cord entanglement.³¹ Thrombosis can also be found in thrombophilic states, fetal chromosomal disorders, toxic agents to fetal vessels, and some viral infections.⁴

Fetal membrane color may also be impacted by maternal diabetes. Fetal membranes and the fetal surface of the chorionic plate are normally clean and transparent producing a blue color on the chorionic plate and pink color on the free membranes. However, in fetal acute chorioamnionitis, another characteristic of diabetic placentas, a diffuse yellow/white–opaque feature is observed with infiltration of granulocytes, lymphocytes, and other inflammatory cells. In addition, meconium staining, also seen in maternal diabetes, may produce a green coloration of the membranes or a brown color if the meconium is accompanied by hemosiderin deposition.³² Because several pathologies may occur simultaneously, the best description of membrane color is often “normal” or “abnormal.” The macroscopic evaluation of the maternal surface of the placenta should demonstrate the normal mosaic of 20–40 cotyledons. This mosaic can be absent in pathologic conditions, such as vascular pathologies causing extensive fibrin deposition. The presence of adherent fresh or old blood clots dissecting the placental parenchyma is indicative of placental abruption. These features are also observed in placentas from patients carrying thrombophilic traits, maternal preeclampsia, or hypertension.

Microscopic evaluation

Placental pathology in pregnancies complicated by maternal diabetes varies based on physiological influences including the type of diabetes, degree of dysglycemia, and insulin use.^{11,21,27} Type 1 diabetes is associated with increased capillary volume and greater degrees of vascular dysfunction, including increased branching and nonbranching angiogenesis, likely the result of increased leakiness of fetal placental vessels.^{21,22} In addition, studies have shown that women with type 1 diabetes have a higher prevalence of placental dysmaturity while women with type 2 diabetes have a higher prevalence of placental infarcts.²¹ Compared to gestational diabetes, pregestational diabetes results in a greater number of histopathologic lesions, such as chorial edema and interstitial hemorrhage,³³ while gestational diabetes has been associated with increased fibrinoid material, villous edema, hyperplasia, and thickening of the basement membrane.³⁴

The literature presents conflicting views regarding the degree to which maternal glycemic control affects placental histopathology. However, in a recent systematic review of the topic,²¹ several studies have shown that both pregestational and gestational diabetes are associated with an increased frequency of placental villous immaturity, even with controlled glycemic levels.^{29,35} Other studies have found that placentas from women with diabetes and well-controlled glucose levels appeared normal when examined by routine light microscopy.^{36,37} A study of an aggregated population of women with pregestational or gestational diabetes stratified by glycemic control revealed that first-trimester “low” HbA1c levels ($\leq 6.0\%$) were associated with more placental infarcts and less villous maturity compared to “high” HbA1c levels ($> 6.0\%$). When excluding the population of women with preeclampsia, only the placental infarct incidence remained significantly different between the two groups.¹¹

Another well-documented effect of maternal diabetes in pregnancy is chorangiosis, described as the presence of 10 or more villi with 10 or more capillaries in 10 or more low-power microscopic fields.^{29,38–43} Chorangiosis is believed to be a response to immature villi, another effect of maternal diabetes during pregnancy.^{29,44–47} Interestingly, one study

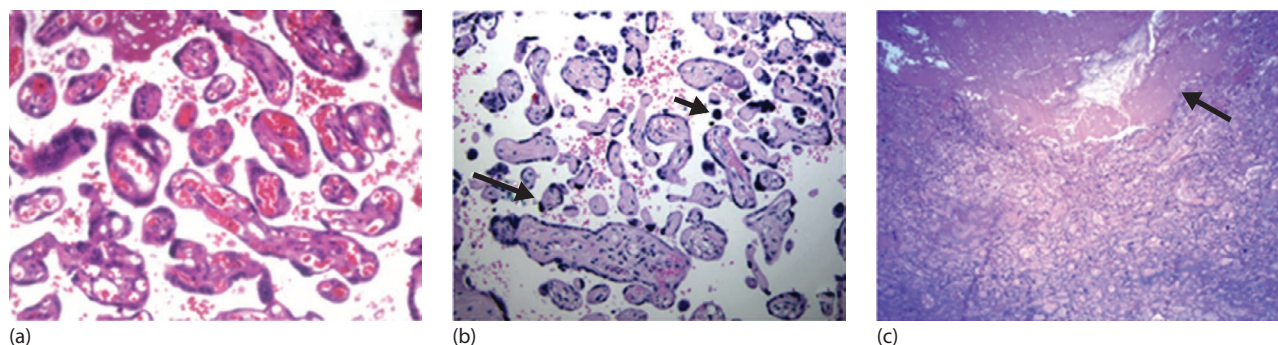


Figure 11.3 Hematoxylin–eosin section of a normal placenta at 38 weeks gestation (a), a placenta at 38 weeks gestation with maternal gestational diabetes (b), and a placenta at 38 weeks gestation with insulin-dependent diabetes (c). Note the smaller villi in (a) have 1–3 capillaries, while those in (b) have 3–5, and in (c) have 10 or more. The villous stroma in (a) is dense and pink and the trophoblast has formed syncytial knots (arrow). The villous vessels are all peripheral (arrowhead). With diabetes, there are few syncytial knots (b and c), and the stroma is more open and clear.

demonstrated a difference in chorangiosis prevalence by race/ethnicity; white women with gestational diabetes had a higher rate of chorangiosis compared to nonwhite women with gestational diabetes.²⁷ Villous immaturity, defined as inadequate or absent terminal villi, can lead to relative hypoxia due to the fact that the centrally located villous capillaries will increase the distance oxygen and nutrients need to travel from the maternal to fetal circulation.⁴⁸

Chronic chorioamnionitis may also be present in the diabetic placenta. This finding is characterized by infiltration of the membranes, chorionic plate, and umbilical cord by mature lymphocytes, plasma cells, and histiocytes.^{49,50} Although chronic chorioamnionitis may be seen in the setting of infectious agents, other suggested mechanisms have included an imbalance of the systemic inflammatory milieu associated with insulin resistance in gestational diabetes mellitus.⁵¹ In contrast to fetal acute chorioamnionitis, chronic chorioamnionitis is usually associated with villitis of unknown etiology and cannot be evaluated via gross examination.⁵²

One of the more common diseases associated with maternal diabetes is hypertension. Whether pregnancy related, such as preeclampsia or pregnancy-induced hypertension, or pregestational, hypertension can cause vascular damage to the uterus leading to poor blood flow to the placenta. The resulting uteroplacental insufficiency causes placental ischemia that is associated with infarction, chronic and acute abruption, and stunted placental growth. This impaired placental growth is associated with a small organ, weighing less than the 10th percentile, and accelerated villous branching, also referred to as hypermaturity (Figure 11.2).⁵³ In addition, hypertensive diabetic placentas have more syncytial knots, more vasculosyncytial membranes, smaller villi, centrally located villous vessels, and decreased vessels per villous compared to placentas from nonhypertensive diabetic pregnancies (Figure 11.3). Poor glucose control will exacerbate these findings and result in placentomegaly and macrosomia.⁵⁴

Fungal placentitis, a relatively uncommon finding, is also increased in the setting of maternal diabetes.^{55–61} This

pathology includes brisk funisitis or umbilical cord vasculitis with peripheral umbilical cord abscesses (Figure 11.4).⁵⁹ The presence of invasive hyphae within the Wharton's jelly of the umbilical cord is thought to represent an increased risk for disseminated disease in the fetus, but even deeply invasive hyphae are usually benign.³ Consequently, it usually does not have significant sequelae for the fetus, although rarely fungal placentitis can lead to overwhelming sepsis.^{62,63}

Fungal infection may also promote umbilical cord vasculitis and abscess formation, also associated with acute chorioamnionitis. The abscesses typically have easily identifiable hyphae invading the Wharton's jelly or superficial hyphae and do not require special stains for visualization. Abscesses on the surface of the umbilical cord are nearly always due to *Candida* although they can be occasionally observed in group B β -hemolytic *Streptococcal* infections. When visible hyphae are absent, fungal specific staining such as silver stains should be used.

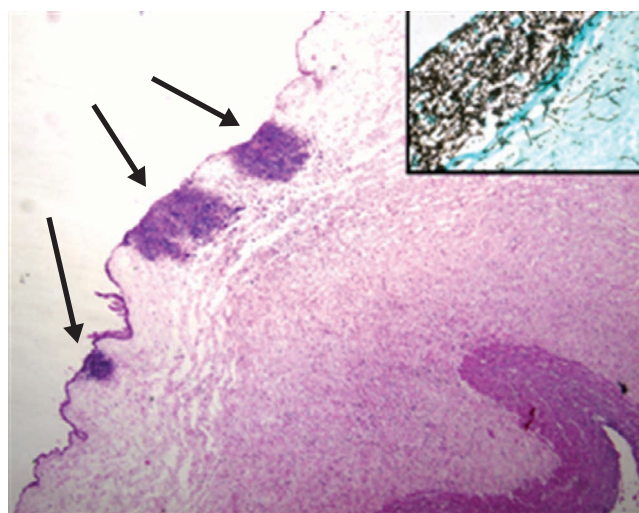


Figure 11.4 Hematoxylin–eosin section of an umbilical cord showing peripheral abscesses (arrow) that contain maternal white blood cells and abundant candidal forms (insert with silver stain).

Conclusions

The placenta in maternal diabetes is heavy, large, somewhat immature, and characterized by chorangiosis and vascular anomalies such as decidual vasculopathy. Increased vascular damage results in uteroplacental insufficiency, reduced placental growth, and villous hypermaturity, a pathologic profile similar to that observed in hypertension during pregnancy. Placental pathologic characteristics have been shown

to be influenced by the type of diabetes and degree of dysglycemia, but more research is required to elucidate the roles of demographic factors, such as race/ethnicity, and clinical characteristics, such as insulin use. Based on the interaction of these and additional genetic and environmental factors, increased risk for villitis, chorioamnionitis, and funisitis may exist. Further research into the pathology associated with diabetes is warranted to enhance our understanding of clinically relevant diagnostic and management information.

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12 The great obstetric syndromes: The roots of disease

Rinat Gabbay-Benziv and Ahmet A. Baschat

Introduction

The term “great obstetrical syndromes” was originally applied to pregnancy-related disorders such as preterm labor, preterm premature rupture of membranes, preeclampsia, spontaneous pregnancy loss, stillbirth, and abnormally delayed or accelerated fetal growth. All of them share a placental component as part of their etiology.¹ The underlying concept is one of multiple underlying etiologies that adversely interact with the maternal–fetal unit to initiate subclinical pathology that progresses to clinical manifestation that also results in fetal adverse outcome. This concept is applicable to conditions such as gestational diabetes mellitus (GDM): a metabolic disease where the combination of maternal predisposition and placental factors results in progressively impaired glucose tolerance with secondary maternal and fetal effects that typically manifest in the third trimester.^{2–4} Understanding the contributory role of these interactions is important for prediction, screening, diagnosis, prognosis, and ultimately therapeutic interventions.

This chapter aims to review the changes in maternal–placental–fetal interface associated with normal glucose metabolism and the shift to abnormal glucose metabolism up to the clinical threshold of GDM with an emphasis on the periconception period, early gestation, and adaptive mechanisms throughout pregnancy and their relationship to the evolution of disease.

Periconception interactions

The placenta interfaces the maternal and fetal compartments, and in the first trimester, placenta-mediated maternal adaptations ensure preferential nutritional supply to the placenta and fetus. This is achieved through a metabolic state that is characterized by relative increase in insulin resistance and anabolism,⁵ both are linked to the rise in human chorionic gonadotropin (hCG) and human placental lactogen (hPL). This principal change in metabolic handling of nutrients results in higher postprandial glucose levels and increased placental glucose utilization contributing to a rapid fall of fasting glucose levels accompanied by a rise in free fatty acids.^{6,7} While there

is a compensatory increase in pancreatic β cells response and insulin secretion, the opposing effects of placental hormones, cortisol, and progesterone on metabolism remain progressive and prevalent so that the maintenance of placental and fetal nutrition prevails at the expense of maternal glycemic control. It is noteworthy that this metabolic pattern is ubiquitous and independent of maternal physical characteristics but can result in exaggerated metabolic effects in predisposed women. The recognition that pregnancy is a diabetogenic state is based on these metabolic changes that can exceed the threshold to precipitate the development of overt GDM.

Maternal predisposition or hCG-mediated exacerbation?

The damaging potential of increased glucose levels is reflected by the increased rates of early pregnancy loss, placental dysfunction, maternal hypertensive disorders, and congenital birth defects in diabetic women with poor periconception glycemic control.^{8–11} Catalano and colleagues compared longitudinal changes in peripheral insulin sensitivity between lean and obese women with subsequent normal glucose tolerance or GDM from preconception throughout pregnancy using the hyperinsulinemic–euglycemic clamp technique.^{12,13} In these studies, all women experienced a 50%–60% decrease in insulin sensitivity with advancing gestation. The greater degree of insulin resistance that contributed to the development of GDM was attributable to preexisting insulin insensitivity and the superimposed pregnancy-related effect. Both lean and obese women who later on developed GDM had decrease insulin sensitivity prior to pregnancy compared to their matching controls who continued to have normal glucose tolerance in pregnancy. These studies illustrate that GDM arises when the pregnancy-associated metabolic impacts push predisposed women over the threshold that constitutes normal glucose tolerance and that this effect is progressive with advancing gestation. This further implies that the degree of preexisting vulnerability to metabolic deterioration determines the onset and degree of clinical disease and the potential for placental and fetal complications.

Luoto et al.¹⁴ studied the impact of first-trimester dietary modification and physical activity on the prevention of GDM and delivery of a large-for-gestational-age infant. In this study, pregnant women with at least one risk factor for GDM (age > 40, BMI > 25, prior GDM, prior macrosomia, and family history of diabetes) were recruited at 8–12 gestational weeks. Modification of physical activity was initiated at recruitment and dietary consult started at 16–18 gestational weeks. The study demonstrated that the interventions had an impact on infant birth weight but failed to reduce the rate of GDM. This provides further evidence that therapy does not prevent the development of GDM but can reduce the consequences of the condition.

Interaction with placental development

The placenta has many roles. Other than being a selective barrier between the maternal and fetal circulations that is capable of controlling nutrient and gas exchange, it also has immune and endocrine functions. The conditions that contribute to the development of the great obstetrical syndromes exert their effects in part by interfering with normal placental development that sets the stage for the development of pregnancy-related hypertensive disease, preterm delivery, stillbirth, abruption, and disrupted fetal growth.³

GDM is associated with maternal and fetal short-term and long-term complications. Well-recognized complications are the increased risk for type 2 diabetes for the mother and accelerated growth for the fetus. Although less common, but not less important are fetal adverse outcomes such as stillbirth, delivery complications attributable to macrosomia, and neonatal metabolic complications. Late-onset metabolic complications for the offspring are associated with endothelial/vascular dysfunction that may later cause obesity, hypertension, type 2 diabetes mellitus, and metabolic syndrome. At least some of these complications may be related to aberrant placental structure or function caused by the metabolic milieu of the diabetic mother.

An important question is how early in gestation can placental changes related to diabetes be seen. Following fertilization, placentation is initiated when the trophoblast develops as a cell area that is distinct from the inner cell mass that will form the embryo. The progenitor cytotrophoblast cell is the stem cell of the placenta. These cells proliferate throughout gestation, differentiating along two pathways to form villous cytotrophoblast that ultimately will become either syncytiotrophoblasts (outer cellular layer) or extravillous cytotrophoblasts (inner cellular layer). The syncytiotrophoblast has several functions, including transport of gases, nutrients, and waste products and synthesis of peptide and steroid hormones that regulate placental, fetal, and maternal systems. The extravillous trophoblast (EVT) has a proliferative component and an invasive component. Invasive EVT that invades the decidua is called interstitial EVT, whereas EVT that invades and remodels the spiral arteries is called the endovascular EVT. Endovascular invasion (intramural

or intra-arterial) results in displacement of vascular smooth muscle and endothelial cells and transforms the narrow spiral arteries into a low-resistance high-capacity vascular bed.

Diabetic placenta

The term GDM encompasses all women first discovered in pregnancy and accordingly by itself does not distinguish between diabetes exclusively precipitated by pregnancy from preexisting type 2 diabetes incidentally discovered during pregnancy. In fact, in 30%–40% of women with GDM, the diagnosis is made prior to 20 weeks of gestation,^{15,16} increasing the likelihood that there is an overlap with preexisting type 2 diabetes. In principle, the disruption of normal placental development is most profound if it occurs early in gestation. Because early disruption of development occurs at a time when structural development, especially of the vasculature, is still incomplete, structural and functional placental dysfunction may ensue. In comparison, later development of abnormal glycemic status is more likely to affect the functionality of the placenta. The relationship between the degree of glycemic control and placental changes remains unclear. While some studies support the concept that the degree of damage is proportional to the degree of hyperglycemia, others have shown that even in tight glycemic control there are still histological differences in the diabetic placentas compared to the nondiabetic ones.^{17–19}

Macroscopically, the diabetic placenta is characterized by increased size and weight resulting in an increased placental-to-fetal-weight ratio.^{20–25} These changes are proportional to the degree of hyperglycemia and suggest that in the diabetic environment, the placenta grows first and then contributes to accelerated fetal growth by increased glucose as well as other nutrient transfer.

Microscopically, a number of lesions have been found in increased frequency in placentas of diabetic women compared to controls. Villous fibrinoid necrosis, a condition where villous stroma is replaced by fibrinoid material, and villous immaturity with a decreased formation of terminal villi are observed. These changes may affect maternal–fetal nutrient delivery and gas exchange and accordingly may be precursors to otherwise unanticipated fetal complications such as stillbirth.^{26,27} Chorangiomas and vascular hyperplasia of the chorionic villi are defined as the occurrence of 10 or more villi with 10 or more capillaries in 10 or lower-power microscopic fields and may be a result of increased vascular recruitment that occurs with placental overgrowth. Infarction of 10% or more of the placenta and evidence of ischemia (Tenney–Parker changes) resulting in increased maturation of branching villi and increased numbers of fetal nucleated red blood cells as a marker of chronic fetal hypoxemia are also more commonly seen in the placentas of diabetic women.

Jones et al.²⁸ suggested that even optimal glycemic control cannot abolish the placental effect as they have observed various degrees of changes in the syncytiotrophoblast, cytotrophoblast, trophoblastic basement membrane, and fetal vessels in six out of seven women with all ranges of

diabetic severity. Madazli et al.¹⁷ compared the histology of 22 placentas from women with well-controlled GDM to 22 placentas from nondiabetic women that served as control. They found a sixfold increase in villous immaturity and chorangiosis and a threefold increase in ischemic changes in the placentas of women diagnosed with GDM. These findings were confirmed by the study of Daskalakis et al.,²⁰ which examined a large number of placentas by a pathologist that was blinded to the maternal glycemic status. This study showed that GDM was associated with villous immaturity, chorangiosis, villous fibrinoid necrosis, and nucleated red blood cells regardless of the maternal glycemic status.

Collectively, these studies document that the glycemic control can have profound impacts on many critical developmental and functional aspects of the placenta. Interference with angiogenesis sets the stage for maternal hypertensive disorders. The placenta that is subjected to the opposing stimuli of glucose-mediated growth acceleration and decrease in vascular development is at risk for local ischemic changes. The increased intervillous

diffusion distance of immature villi and the placental size to perfusion mismatch may predispose the fetus to sudden changes in gas and nutrient exchange. Accordingly, the placenta “becomes its own enemy” by initiating the sequence that leads from altered glycemic status to placental dysfunction. Understanding these pathways in greater detail will become important in modifying this sequence of events.

Conclusions

GDM can be regarded as one of the great obstetric syndromes where early placental development coupled with maternal predisposition initiates a chain of events that affects placental, maternal, and fetal development with lasting impacts on mother and child. Understanding the pathways that mediate these effects to greater detail will be required to develop effective screening, prevention, and management approaches.

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13 Placental origins of diabetes and the origin of preeclampsia

Gernot Desoye and Berthold Huppertz

Introduction

The placenta is a fetal organ that early in gestation rapidly develops through a series of essential steps. These encompass

- Anchoring of the placenta to the maternal decidua
- Opening of uterine glands to enable nutrient supply of the embryo during the first trimester of pregnancy, prior to onset of maternal blood flow
- Subsequent opening of spiral arteries to increase oxygen and nutrient supply to the fetus starting with the beginning of the second trimester
- Establishing villous structures and the first primitive vascular plexus within the placenta independent of vasculogenesis within the embryo proper

Given the necessity to rapidly establish the uteroplacental vascular connection as well as the vasculature between embryo and placenta and because of the complex nature of the biological processes driving implantation, placentation, and embryo development, early gestation is a period of high vulnerability of both the placenta and embryo. Although tightly controlled by a variety of mechanisms, each of these processes can malfunction, which in certain situations may lead to impaired placental function later in pregnancy, which could manifest in pregnancy conditions such as preeclampsia and/or fetal growth restriction (FGR).

Its localization between the maternal and fetal blood systems makes obvious the essential contribution of the placenta to the fetal environment and thus fetal growth and development by mediating transfer of maternal nutrients. As the placenta is exposed to changes in both the maternal and the fetal circulation, one can expect that placental structure and function are altered in pregnancy conditions associated with changes in the maternal environment such as in maternal diabetes.

This chapter will discuss the intense interplay between the mother and fetus and the role of the placenta as mediator. Maternal changes may lead to placental

changes, which are essential for determining the fetal phenotype in maternal diabetes, while intrinsic placental changes may determine the maternal phenotype (preeclampsia) and/or the fetal phenotype (FGR). All of these changes will have long-term consequences for the fetus and childhood development as well as maternal health later in life.

Diabetes

Diabetes and obesity share several features such as insulin resistance, dyslipidemia, and inflammation. The term “diabetes” was coined to reflect these commonalities. The prevalence of diabetes is increasing dramatically.^{1,2} Especially alarming is that the percentage of overweight or obese children is now above 20% in Europe.³ Therefore, childhood obesity is one of the greatest current challenges.⁴ It leads to an increasing number of individuals developing type 2 diabetes mellitus (T2DM) and other metabolic diseases early in life⁵ and therefore has become of considerable public health concern.³ Childhood obesity in girls increases their risk to develop diabetes prior to or within their pregnancy giving birth to offspring with again a higher risk for developing diabetes later in their life, creating a self-perpetuating situation.

The rise in the prevalence and severity of early-life diabetes has a multifactorial background, where complex interactions between genetic and environmental factors contribute.⁶ These interactions are dynamic with a strong effect during critical periods of development in prenatal and early postnatal life. The first mechanistic principle of this environment-dependent programming with a long-term impact on health later in life was postulated in the 1970s of the last century.⁷ Since then, more detailed concepts have been developed trying to explain the association between later disease risk and fetal overnutrition (“fuel-mediated in utero hypothesis”), fetal undernutrition and postnatal overnutrition (“mismatch hypothesis”), and postnatal overnutrition (“accelerated postnatal growth hypothesis”).⁸ Recently, a unifying concept has been proposed.⁹ All these

concepts ultimately explain why and how diabetes and/or obesity may develop later in life.

A key role is attributed to the intrauterine environment, in which the fetus grows and develops. This intrauterine environment is characterized and determined by the concentrations of principle nutrients, cytokines, growth factors, and hormones.

Placenta in diabetes

How the placenta integrates maternal and fetal exposures¹⁰ has been the subject of several reviews.^{11–24} It is unclear whether any of these placental changes are causally linked with the fetal and neonatal phenotype of pregnancies in diabetes. Therefore, we will focus on the specific concept that fetal and neonatal insulin plays a central role in determining the neonatal phenotype²⁵ and represents the mechanistic link with childhood diabetes and associated comorbidities.²⁶ By emphasizing on the maternal and fetal glucose/insulin axis and its effects on placenta and fetus, we will explain the fetal phenotype and some aspects of intrauterine programming of childhood obesity in the wake of maternal diabetes.

The fetus/neonate in maternal diabetes

A growing body of evidence shows that the major difference in the neonatal phenotype between normal and diabetic/obese pregnancies is the fetal body composition independent of birth weight. While the fat-free mass is unaltered, neonates of diabetes pregnancies contain more fat. These differences are found even when born in the appropriate-for-gestational-age range (between the 5th/10th and 90th birth weight percentile).^{27–30} Interestingly, gestational diabetes mellitus (GDM) and maternal obesity are independent risk factors for neonatal body fat and contribute additively.³¹

The relative body fat of the neonate associates with that of the offspring at age 9 years, whereas total body weights do not associate.³² This reinforces the concept that the number of adipocytes for a human being is determined very early in the life cycle if not already in utero.³³ The trajectory of adipocyte number cannot be changed not even when weight, i.e., fat, is lost. Thus, once the growing fetus has developed more adipocytes in the wake of the diabetes environment, then the neonate may be strongly disposed to remain on this trajectory and have more adipocytes also in childhood.

According to the well-established Pedersen hypothesis, maternal hyperglycemia will lead to fetal hyperglycemia. As a result, fetal islets will become hypertrophic and hypersecrete insulin.³⁴

The hyperinsulinism may not only be the result of fetal hyperglycemia, because some amino acids such as arginine can also stimulate insulin secretion, especially from the overactive fetal pancreas as in maternal diabetes.³⁵

Transplacental transport of nutrients in diabetes

Insulin secretagogues

The placenta is richly endowed with glucose transporters foremost with GLUT1,³⁶ which are dynamically regulated across gestation.³⁷ These confer a high glucose transport capacity, which only becomes saturated at a maternal–fetal glucose concentration difference of 20–25 mM D-glucose.³⁸ This overcapacity to transport glucose renders the placenta relatively insensitive to glucose transporter changes as they may occur in diabetes³⁹ induced by hyperglycemia^{40,41} and other components of the intrauterine environment.⁴² In fact, direct measurements of maternal-to-fetal glucose transfer in placentas from normal and gestational diabetic pregnancies did not find differences.^{43–45} Thus the placenta per se does neither limit nor promote glucose flux at least at the end of gestation. The amount of glucose reaching the fetal circulation is thus dictated by its maternal–fetal concentration gradient with some contribution of uteroplacental and fetoplacental blood flow.⁴⁶

Arginine uptake into various placental cells has been studied, because of its precursor role for NO biosynthesis. Glucose as well as insulin is capable of stimulating arginine uptake into a trophoblast model cell line,⁴⁷ which may suggest alterations associated with maternal diabetes mellitus. However, trophoblast uptake does not necessarily correspond with overall transfer. There are no data available on transplacental arginine transport and potential changes in maternal diabetes mellitus. Arginine concentrations in the maternal circulation are higher in diabetes mellitus as compared to nondiabetic pregnancies, and this likely leads to an increase in the fetus. This increase must be transient, because fetal steady-state concentrations of arginine are unchanged in diabetes.⁴⁸ The transient rise in fetal arginine elicits a pancreatic response as reflected by elevated insulin levels.⁴⁹ This response is, however, limited to diabetic pregnancies, which is an indication of the accelerated β -cell maturation under the conditions of permanent overstimulation by glucose and perhaps arginine.

Lipids

The augmented fat accretion in offspring born to diabetes or obesity pregnancies has sparked interest in the question whether there is an increased transfer of lipids across the placenta under these conditions to contribute to the buildup of fetal fat depots.^{50,51} Lipids are a complex class of molecules most of which contain fatty acids as esters such as triglycerides (TGs), phospholipids, and cholesterol esters. These in turn are building blocks for lipoproteins, in which more than 95% of fatty acids are bound.

The lipoproteins have to be hydrolyzed by lipases to release fatty acids, which is the lipid moiety transported to the fetus. For topological reasons, these lipases have to be located on the microvillous membrane of the syncytiotrophoblast. For most fatty acids, a maternal–fetal concentration gradient

exists, and hence, free fatty acids may traverse the placenta by simple diffusion, but an intermediate esterification of free fatty acids to TGs within the placenta may occur, followed by lipolysis and release into the fetal circulation. Lipid stores in the placenta are elevated in diabetes.^{52,53} It is unknown whether this affects overall fatty acid transfer.

Endothelial lipase (EL), a close relative of lipoprotein lipase (LPL), was recently identified on the microvillous syncytiotrophoblast membrane at the end of gestation (Figure 13.1), whereas LPL was found in cells subjacent to the fetoplacental endothelium.⁵⁴ EL is upregulated in placentas from obese women with GDM, but unchanged in placentas from lean GDM cases.⁵⁵ This suggests that metabolic inflammation together with diabetic conditions accounted for dysregulation of EL in pregnancies complicated by obesity and GDM. TNF- α and leptin, both inflammatory cytokines often elevated in diabetes, are putative key regulators of EL.

After hydrolysis and release of fatty acids, they have to be transported across the placenta to ultimately reach the fetal circulation. The transport will be accomplished by a range of fatty acid transporters present on the surface and of fatty acid-binding proteins in the cytoplasm of placental cells.^{56–58} Each of these has a different preference for the various individual fatty acids and may be subject to regulation by distinct changes in the diabetes environment.^{59,60}

Notwithstanding the presumed key role of EL in hydrolyzing maternal lipoproteins on the placental surface and the fatty acid transporters for transplacental movement of fatty acids, it is unclear whether total placental EL activity or the transporter activity is the limiting and therefore determining factor for overall fatty acid transport. Moreover, it

is also unknown whether overall transfer of the lipoprotein-borne fatty acid is altered in diabetes.

Effect of fetal hyperinsulinism

Fetal hyperinsulinism as it often occurs in diabetes has several effects, which may not only help sustain fetal development and growth but also mediate long-term consequences associated with intrauterine exposure to the diabetes environment (Figure 13.2).

Fetal metabolism and uptake of glucose and fatty acids

Glucose uptake into fetal tissues is stimulated by hyperinsulinism as reflected by a higher glucose disappearance rate (“k-value”) in newborns of diabetic as compared to nondiabetic pregnancies.³⁴ The insulin-stimulated glucose uptake will transiently decrease glucose levels in the fetal circulation, thereby steepening the maternal–fetal glucose concentration gradient with ensuing increased glucose flux across the placenta until steady-state concentrations will be reached. At this stage, the amount of glucose passing from mother to fetus is independent of the maternal glucose level and dictated by the fetus. Whether a similar mechanism exists also for fatty acids is unknown. When fatty acid profiles were measured in the cord blood of newborn from gestational diabetic and nondiabetic pregnancies, then lower proportion of polyunsaturated fatty acids were found in gestational diabetic newborn but only in the arterial and not in the venous cord blood. All other fatty acids were similar.⁶¹ This would

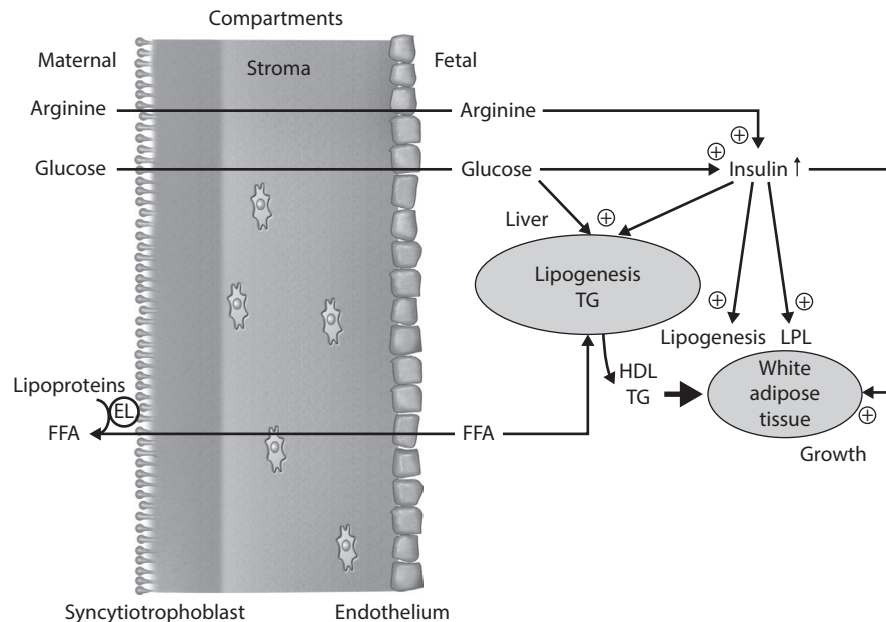


Figure 13.1 The Pedersen–Freinkel concept expanded. Maternal glucose and arginine cross the placenta and stimulate fetal insulin secretion. Lipoprotein–triglycerides (TGs) and phospholipids will be hydrolyzed by lipases such as endothelial lipase present on the microvillous membrane of the syncytiotrophoblast to release fatty acids, which then traverse the placenta to contribute to the fetal fatty acid pool. Fetal glucose and insulin enhance hepatic TG formation. Insulin stimulates growth of adipocytes in white adipose tissue as well as lipoprotein lipase (LPL) transcription. LPL hydrolyzes TGs released from the liver and provides free fatty acids for uptake into adipocytes and reesterification under insulin promotion to ultimately form TGs.

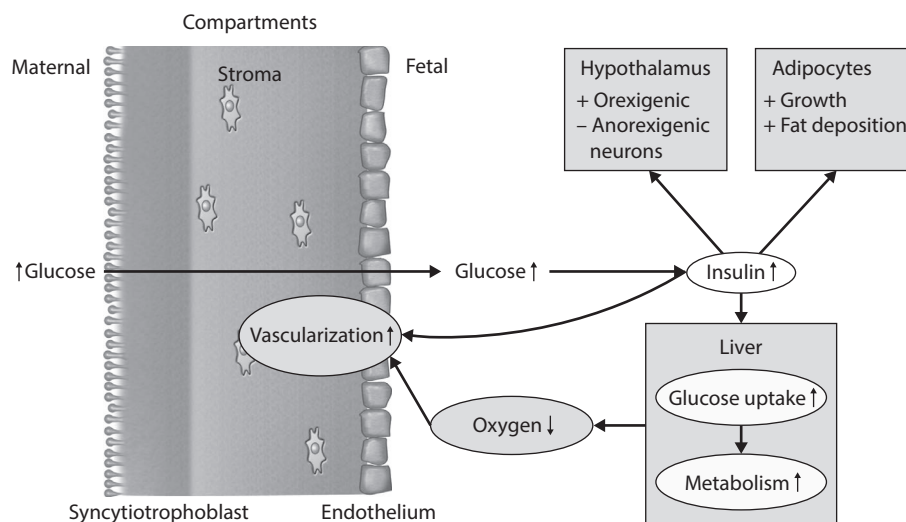


Figure 13.2 Fetal hyperinsulinism leads to multiple changes. High insulin levels promote hepatic glucose metabolism and indirectly glucose uptake into hepatocytes and other insulin-sensitive peripheral tissues. This will increase fetal oxygen demand for aerobic metabolism. In a situation of inadequate oxygen supply, this results in fetal hypoxia. Insulin directly and hypoxia indirectly stimulates angiogenesis-promoting factors, which are potent stimulators of placental angiogenesis serving to ultimately increase the degree of placental vascularization. Insulin also acts on the adipocytes with its dual role as growth factor to stimulate adipocyte growth and as hormone to promote triglyceride formation and fat deposition. The central role of insulin is reflected by stimulating orexigenic and reducing anorexigenic neurons, which may contribute to neonatal overfeeding in such situations.

indicate that the newborn takes up polyunsaturated fatty acids, which are needed in particular for the development of the retina and the brain, and this uptake may be under the regulation of fetal insulin. Insulin also stimulates TG formation in the fetal liver and in the white adipocytes.

Fetal hypoxia

The insulin-stimulated glucose uptake into peripheral tissues and, in the presence of hyperglycemia, also into the liver is accompanied by enhanced aerobic glucose metabolism generating an increased demand for oxygen. At the same time, maternal and placental oxygen supply is impaired, because of more maternal hemoglobin being present in the glycosylated form and thickening of the basement membrane of the syncytiotrophoblast. Occasionally, this is aggravated by reduced uteroplacental and fetoplacental blood flow. Overall this will lead to an imbalance of oxygen demand and supply and chronic fetal hypoxia. A reduction in umbilical oxygen saturation and oxygen content,⁶² enhanced erythropoiesis,⁶³ and elevated cord blood erythropoietin levels⁶⁴ are often manifestations of inadequate oxygen supply.

Placental vascularization

The placenta as a fetal tissue receives fetal signals and adapts its development and function according to fetal needs. This explains why the placenta is often hypervascularized in maternal diabetes.¹³ Corresponding data for maternal obesity are missing. Mechanistically, low oxygen levels may upregulate hypoxia-sensitive proangiogenic factors such as fibroblast growth factor 2, which promotes sprouting angiogenesis and is increased in the placenta and fetal cord blood in diabetic pregnancies.^{65,66} Fetal insulin may also be capable of directly stimulating placental angiogenesis at least at the

end of gestation, when its levels in the umbilical cord are associated with the capillary surface area.^{20,67} In vitro experiments using primary human fetoplacental endothelial cells also demonstrated insulin stimulation of several pathways involved in angiogenesis.^{68,69}

Fetal hypothalamus

The human brain contains insulin receptors in various regions.⁷⁰ During fetal development, insulin binding to brain receptors increases as the fetus grows, i.e., with advancing gestational age.⁷¹ One of the sites in the brain susceptible to insulin action is the hypothalamus. Insulin exerts neurotrophic functions and contributes to the organization of neuronal networks during critical periods of hypothalamic development.^{72–74} Thus, fetal hyperinsulinism is likely to affect the development of hypothalamus. Indeed in rat experiments, fetal hyperinsulinism was accompanied by increased insulin concentrations in the immature brain⁷⁵ with subsequent permanent dysplasia and neuronal hypotrophy of the ventromedial hypothalamic nucleus.⁹ The prolonged intrauterine exposure to high insulin levels ultimately induces hypothalamic insulin resistance. Since insulin also serves as satiety signal, this may contribute to neonatal overfeeding observed in some mother–offspring pairs. Most recently, maternal hyperglycemia during an oral glucose tolerance test (oGTT) was associated with slower fetal brain responses.⁷⁶

Conclusions

Collectively, fetal hyperinsulinism associated with maternal diabetes not only modifies the classical peripheral insulin-sensitive tissues but also has a broad spectrum of

central effects (Figure 13.2). These effects have been postulated to contribute to the permanently increased disposition to adiposity and associated comorbidities such as T2DM.⁹ Conceptually, this links the placenta and its absence of mechanism to protect the fetus from nutritional overload associated with diabetes, with the medium- to long-term offspring risk for diabetes, and may help explain the trans-generational transmission of diabetes risk.

Origin of preeclampsia

Definition of preeclampsia

Since the cause, development, and etiology of preeclampsia are still far from being clear in a variety of aspects, the syndrome of preeclampsia remains a topic that generates new hypotheses and new research data on a weekly basis. Although the real origin of preeclampsia is still a mystery, it is generally accepted that the placenta rather than the fetus is mandatory for this syndrome to develop. Hence, preeclampsia is based on a dysregulation of the placenta, which in turn leads to the maternal symptoms that define preeclampsia. Here, the interplay between factors released from a dysfunctioning placenta on one hand and the maternal response on the other hand is based on the susceptibility of the mother to placenta-derived factors. This complex interplay finally defines whether or not a pregnant woman develops preeclampsia. Furthermore, time of onset, severity, and progression of preeclampsia into eclampsia all depend on this interaction between the mother and placenta. Thus, even if the origin of preeclampsia lies within the placenta, the interactions between the fetus, placenta, and mother need to be taken into account to define the factors crucial for the onset of maternal symptoms.

Preeclampsia is specific for pregnancy, defined as occurring after 20 weeks of gestation and is characterized by the onset of proteinuria and hypertension in a woman with so far normal blood pressure.⁷⁷ Proteinuria is defined as ≥ 0.3 g protein in 24-hour urine, or 0.1 g/L ($>2+$ on dipstick), while hypertension is defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg.⁷⁷ Additionally, multiple features on top of proteinuria and hypertension may occur and are mostly restricted to the more severe types of the syndrome, including cerebral or visual disturbances, headache, nausea and vomiting, epigastric or right upper quadrant pain, pulmonary edema or cyanosis, oliguria (less than 500 mL urine in 24 hours), impaired liver function, and thrombocytopenia.⁷⁷

The only cure for preeclampsia is still the delivery of the baby (and hence the placenta). So far there is no effective interventional treatment to prevent or even treat preeclampsia. Hence, there is the danger for a woman suffering from preeclampsia to progress into eclampsia, a life-threatening exaggeration associated with tonic-clonic seizures, stroke, and death.

Preeclampsia is one of the major reasons for maternal, fetal, and neonatal mortality and morbidity, and worldwide preeclampsia affects about 2%–8% of all pregnancies, especially in developing countries.^{77,78} Here, preeclampsia accounts for

10%–15% of maternal deaths, 12% of infants born SGA (small for gestational age), and up to 25% of stillbirths and neonatal mortality rates.⁷⁹ Although preeclampsia is pregnancy specific, it has been shown to have long-term consequences for those women who experienced preeclampsia. Such women are at increased risk of a variety of diseases including chronic hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, kidney disease, thromboembolism, hypothyroidism, and even impaired memory.⁸⁰

Stratification of preeclampsia

During the last decade, efforts have been undertaken to stratify preeclampsia into various subtypes and trying to define groups that are more homogeneous in terms of severity, marker expression, and onset of symptoms. One approach used blood pressure values to differentiate between a mild form of preeclampsia (systolic blood pressure between 140 and 160 mmHg and/or diastolic blood pressure between 90 and 110 mmHg) and a severe form of the syndrome (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 110 mmHg). Another approach has used gestational age to define an early-onset type (before 34 weeks of gestation) and a late-onset type (after 34 weeks of gestation).⁸¹

The latter approach in combination with other studies has led to the idea that the early-onset type of preeclampsia is completely different to the late-onset type of the syndrome. At the same time, it has to be stressed that the maternal symptoms of both types are identical and that mild and severe cases of preeclampsia can be found in both types. The major difference between the two types—besides the different gestational age at onset—is the large overlap with FGR in the early-onset group⁸² (Figure 13.3). Hence, the features of preeclampsia *per se* are quite similar in both groups—if the other conditions that cluster around the diagnosis of preeclampsia and that lead to adverse outcomes are not taken into account.⁸³ Today, the notion whether or not the two subtypes are different in terms of their origin is still discussed controversially.

Late-onset type of preeclampsia

Worldwide most of the preeclampsia cases (80% and more⁸⁴) can be attributed to the late-onset type. The onset of symptoms of such cases occurs at a gestational age around the normal time of delivery (≥ 37 weeks of gestation), with most of the neonates showing normal growth without any signs of growth restriction (Figure 13.3). Also the placenta mostly does not show any gross morphological changes and displays normal values for volume and weight. Blood flow from the mother toward the placenta as assessed by uterine artery blood flow and blood flow from the fetus toward the placenta as assessed by umbilical artery blood flow are mostly normal in those cases of late-onset preeclampsia as well.

Hence, it seems as if the late-onset type of preeclampsia—although originating from factors derived from the placenta—is a syndrome that only affects the mother rather than the fetus. Also, pregnancies with an enlarged mass and/or surface of the placenta, such as in diabetes mellitus, multiple pregnancies, anemia, or high altitude, tend to have an increased

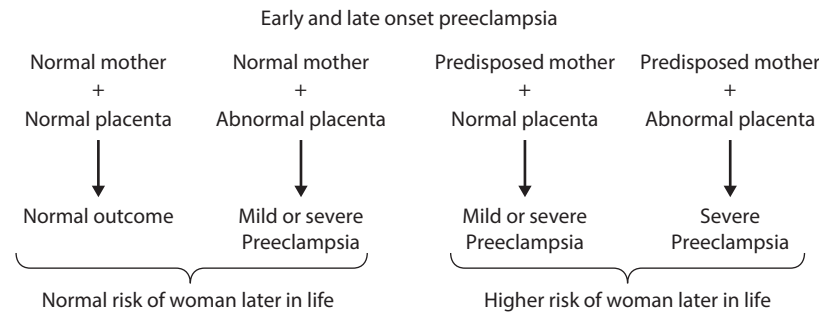


Figure 13.3 Origin of preeclampsia. Representation of a very simplified scheme showing the players and combinations leading to preeclampsia. While the combination of a normal mother with a normal placenta should end in a normal outcome, all of the other combinations may result in preeclampsia. If one player is normal, the syndrome may be mild or severe, while the combination of both being abnormal or predisposed mostly results in severe cases of preeclampsia. In these scenarios, a predisposed mother will also carry a higher risk for, e.g., cardiovascular diseases later in life.

risk to develop the late-onset type of preeclampsia.⁸⁵ Here the question arises whether there needs to be a dysregulation of placental development at all to cause this type of preeclampsia. There may well be cases where an increased maternal susceptibility in combination with an inadequate maternal response to placenta-derived factors could lead to preeclampsia without any dysfunctional placental deterioration.⁸² However, respective data are missing.

Early-onset type of preeclampsia

Different to the late-onset type of preeclampsia, the early-onset type of the syndrome only develops in a small proportion of all preeclampsia cases, in 5%–20%⁸⁴ (Figure 13.4). Early-onset preeclampsia only affects 1 in 200 pregnancies; however, at the same time, it is responsible for the majority of fetal and maternal morbidity and mortality in the developed world that are related to preeclampsia.⁸⁶

It is not only the gestational age at the onset of symptoms that makes the early-onset type different to the late-onset type. The early-onset cases are mostly associated with growth restriction of the fetus. This is why the early-onset type is recognized as showing features not present in the late-onset type.

However, features thought to be specific for early-onset preeclampsia such as changes of blood flow within the maternal uterine arteries or even abnormal blood flow in the umbilical arteries are regular findings in cases with pure FGR.

Hence, a dispute arose whether these findings are directly related to early-onset preeclampsia or whether there is an overlap of two independent syndromes, FGR and preeclampsia.⁸² From a clinical point of view, this dispute is of no relevance. In a clinical setting, it is important to do the best for both, mother and child. Here it does not play a role whether there are two independent syndromes or just one with features of both. However, scientifically it indeed plays an important role since only a clear demarcation between FGR and preeclampsia will help to identify the origins of both syndromes.

Definition of FGR

FGR affects 5% of all pregnancies and is one of the leading causes of perinatal mortality and morbidity.^{87–89} In literature, several terms are used in parallel, leading to massive confusion. The terms fetal growth restriction and intrauterine growth restriction (IUGR) are synonymous and can be used to describe the same issue: a fetus who has not been

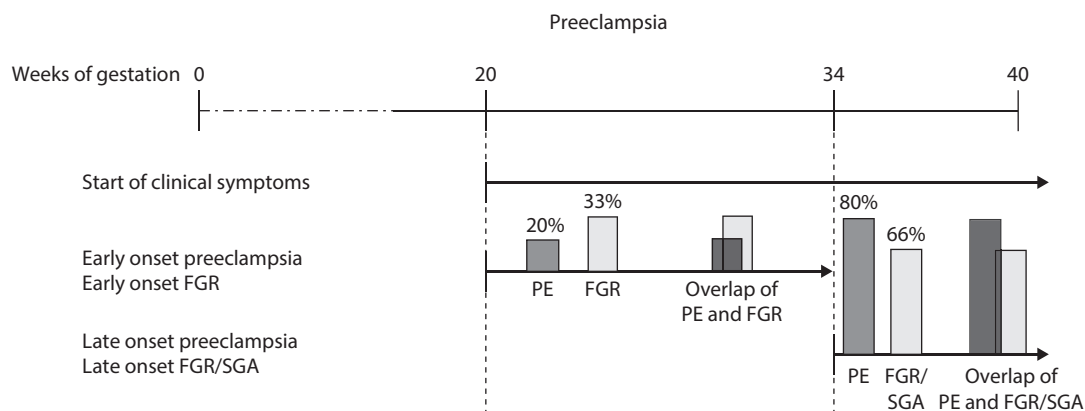


Figure 13.4 Early-onset versus late-onset preeclampsia. Schematic representation of the length of pregnancy in weeks (0–40) with two specific time points: 20 weeks of gestation as the start of clinical symptoms of preeclampsia (per definition) and 34 weeks to discriminate between early-onset (prior to 34 weeks) and late-onset (after 34 weeks) preeclampsia. The two types of preeclampsia and fetal growth restriction (FGR) are further characterized by their occurrence rates in all preeclampsia and FGR cases (% values) and also by their massive overlap in early-onset cases and their negligible overlap in late-onset cases. In late-onset cases, it is still very difficult to achieve a clear distinction between FGR and small-for-gestational-age cases without growth restriction.

able to achieve its growth potential.⁹⁰ These two terms (fetal growth restriction and intrauterine growth restriction) are regularly mixed with the term small for gestational age and are even used as synonyms. However, fetuses who are SGA are defined being born below a certain growth percentile (e.g., below the 10th percentile). Not all of such fetuses are also growth restricted since there are fetuses with a normal growth trajectory but who are constitutionally small while otherwise normal.^{89,90} Ott has calculated that of 100 SGA babies with a growth below the 10th percentile, only 30 are growth restricted and hence are FGR.⁹¹

Furthermore, FGR can also appear with a baby being born above the 10th percentile. In such cases, the growth trajectory of a fetus did not remain constant over the duration of pregnancy but rather massively declined (e.g., from the 70th percentile to the 30th percentile). Also such newborn babies are growth restricted without being SGA.^{90,92}

Features of preeclampsia and FGR

The clinically relevant features of early-onset preeclampsia (excluding hypertension and proteinuria of the mother) may be caused by preeclampsia or may be the features of the overlying syndrome FGR.⁸² This deleterious combination of early-onset FGR and early-onset preeclampsia dramatically increases the risk for both, mother and baby. This is why these cases are highly relevant for clinical intervention.

The idea that there are two overlapping syndromes rather than a single syndrome with both features is supported by a variety of studies and data:

1. In cases with preeclampsia, the placenta does not display any gross morphological changes and also shows normal values for volume and weight. Of course, a macroscopically normal placenta does not necessarily reflect a histologically and functionally normal placenta. Looking into the morphology of the placenta, also here preeclampsia has only modest effects, if at all. There have been a number of variables that have been quantified using stereological techniques, including placental weight and volume, length, diameter, volume and surface area of villi, villous components and vasculature,^{93–95} and villous domains and intervillous pores.⁹⁶ All of the aforementioned measures were not different between healthy control placentas and those from preeclampsia cases (without FGR). In the presence of FGR, these measures were significantly different, whether or not such cases were further suffering from preeclampsia.
2. Studies predicting preeclampsia and/or FGR using Doppler ultrasound to assess blood flow in uterine arteries showed that again it is FGR rather than preeclampsia that is the effective component here. Nicolaides et al.⁹⁷ have assessed uterine artery blood flow between 11 +0 and 13 +6 weeks by Doppler ultrasound. These authors were able to calculate a detection rate for early-onset preeclampsia of only 40% at a 10% false-positive rate.⁹⁷ Pilalis et al.⁹⁸ used a similar approach and assessed uterine artery blood flow using

Doppler ultrasound between 11 and 14 weeks of gestation. These authors were able to calculate a sensitivity to predict early-onset preeclampsia of only 33.3%, while the sensitivity to predict all cases of preeclampsia (early and late onset) further decreased to 21%. At the same time, the sensitivity to predict early-onset FGR was 100% using the same pool of women.⁹⁸

Etiology of preeclampsia

The etiology of preeclampsia is still unclear, but as described earlier, the placenta is essential. Without the placenta, preeclampsia does not develop. Only the presence of at least one of the two, defective placenta and/or a predisposed mother, may result in preeclampsia.⁸²

Even today it is more than difficult not only to exactly define the syndrome of preeclampsia but also to define the individual that is responsible for the development of the syndrome (mother or fetus). Thus, preeclampsia may derive from at least three different combinations of mother and fetus/placenta (Figure 13.5).

Cases with a normal placenta and a predisposed mother
Here the mother suffers from an inadequate response system and may simply be overloaded by the normal release of factors from the placenta. Today, a number of factors leading to predisposition are defined as risk factors to increase the risk to develop preeclampsia including chronic hypertension or renal disease.

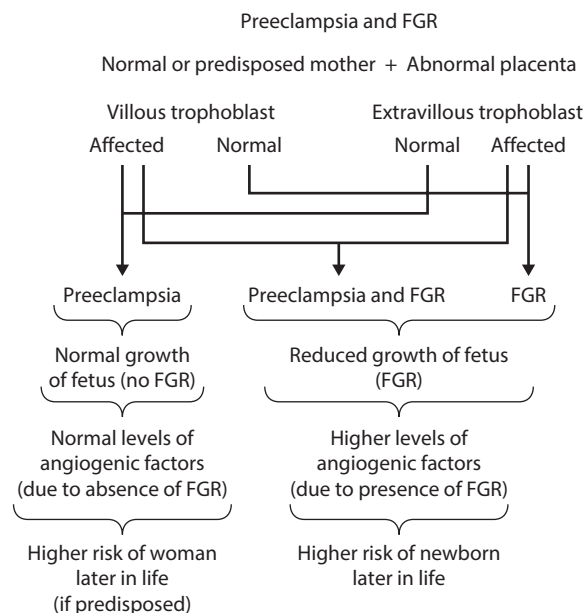


Figure 13.5 Combinations of fetal growth restriction (FGR) and preeclampsia. As described earlier,⁸² preeclampsia could be derived from a dysfunctional villous trophoblast, while FGR could be derived from a maldeveloped extravillous trophoblast. The combinations of these defects in a single placenta determine whether only preeclampsia, only FGR, or the combination of both develops. This may have direct effects on fetal growth and outcome, changes in biomarkers such as angiogenic factors, and long-term effects on the mother or offspring.

The overload of the maternal system may develop slowly resulting in normally grown babies (no FGR), clinical symptoms appearing mostly late in pregnancy (late-onset preeclampsia), and the absence of changes of predictive angiogenic markers such as PlGF and sFlt-1 prior to the onset of symptoms.⁹⁹

Such women may well be the ones who suffer from a higher risk to develop cardiovascular diseases later in life.

Cases with a dysfunctioning placenta and a normal mother

Here, it seems as if mostly the villous syncytiotrophoblast is affected, releasing factors systemically harming the maternal vascular system during pregnancy finally leading to the clinical symptoms of preeclampsia. The syncytiotrophoblast does no longer release most of the factors by controlled secretion and apoptotic shedding. Rather, necrosis and aponecrosis^{82,100,101} result in the release of subcellular fragments and micro- and nanoparticles^{102,103} systemically affecting the maternal endothelium.¹⁰⁴

The normal maternal system may resist any deleterious changes for a longer time period, and hence clinical symptoms may develop only later in pregnancy (late-onset preeclampsia) and in the absence of changes of predictive angiogenic markers such as PlGF and sFlt-1.⁹⁹ Also the fetus may develop into a normally grown baby (no FGR).

The mother may recover completely after delivery without any further long-term effects.

Cases with a maldeveloped and dysfunctioning placenta and a predisposed mother

These are the most severe cases since the combination of both defects will definitively increase the severity of the symptoms of the mother.

A small proportion of these maldeveloped placentas may only show alterations of the syncytiotrophoblast. In those cases, the villous syncytiotrophoblast is affected and releases factors by necrotic and aponecrotic shedding, subsequently affecting a maternal system that is already impaired. The overload of the maternal system will develop fast, and hence clinical

symptoms will appear early in pregnancy (early-onset preeclampsia) with no effect on the growth of the fetus (no FGR) and the absence of changes in predictive angiogenic markers.

However, a larger proportion of these maldeveloped placentas may also show defects in extravillous trophoblast development and hence may additionally result in impaired trophoblast invasion.¹⁰⁵ In those cases, the villous syncytiotrophoblast is affected and releases factors by necrotic and aponecrotic shedding, while the maldevelopment of the extravillous trophoblast will alter maternal blood flow toward the placenta¹⁰⁶ subsequently impairing fetal growth. Again, the overload of the maternal system will develop early in pregnancy (early-onset preeclampsia), growth of the fetus will be impaired as well (FGR), and changes in predictive angiogenic markers will be quite striking.¹⁰⁷

Again, such women may well suffer from a higher risk to develop cardiovascular diseases and other morbidities later in life. In cases with FGR, the babies may show fetal programming as well.^{108,109}

Conclusions

Preeclampsia and FGR are different syndromes that have different etiologies. Both may start as impaired development of the placenta affecting different cell populations and tissues within the placenta. FGR may develop on its own only affecting the fetus without any disturbance found in the mother. The same is true for preeclampsia that only affects the mother without any changes of the fetus. It has to be considered that preeclampsia may be solely derived from a predisposed mother who cannot respond to normally released placental factors in a proper way and hence develops preeclampsia in the presence of a normal placenta.

The different origins and pathways of the etiology of preeclampsia in combination with the simultaneous occurrence of FGR clearly hinder the further progress in identifying the origins of the syndrome. It would be ideal to have markers in hand distinguishing between the different origins and combinations of preeclampsia.

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14 Diagnosis of gestational diabetes mellitus

Donald R. Coustan and Boyd E. Metzger

History

Gestational diabetes mellitus (GDM) is generally considered to be carbohydrate intolerance with variable severity with onset or first recognition during pregnancy. The concept that pregnancy may bring about alterations of carbohydrate metabolism goes back more than 140 years. In 1882, J. Mathews Duncan described what would later be called GDM, indicating that “diabetes may occur only during pregnancy being absent at other times or may cease with the termination of pregnancy recurring sometime afterwards.”¹ In 1946, Miller observed that perinatal mortality was increased in the previous pregnancies of women with diabetes,² and in 1952 Jackson noted a high likelihood of previous stillbirth and fetal macrosomia in women with diabetes.³ A few years later, Carrington coined the term “gestational diabetes.”⁴ In the middle of the twentieth century, one commonly used set of diagnostic criteria for diabetes in the United States was that put forth by the U.S. Public Health Service (USPHS)⁵: a 100 g, 3-hour oral glucose tolerance test (OGTT) was administered. Diabetes was diagnosed if both the fasting and 3-hour whole blood glucose values were ≥ 130 mg/dL or if one of these two was elevated and, in addition, either the 1-hour value was ≥ 195 mg/dL or the 2-hour value was ≥ 140 mg/dL.

In 1964, O’Sullivan and Mahan published their classic treatise recommending pregnancy-specific glucose tolerance test criteria. Noting that pregnancy changes carbohydrate metabolism, such that glucose tolerance test norms might be altered, they described the results of 100 g, 3-hour OGTTs administered to 752 unselected pregnant women, predominantly in the late second or early third trimester. They considered potential diagnostic cutoffs at one, two, and three standard deviations above the means for each of the four blood glucose determinations. The three sets of thresholds were then applied retrospectively to a second dataset of OGTTs in 1333 previous pregnancies, with the outcome variable being the development of diabetes within 8 years of the index pregnancies. These subjects had been followed with periodic OGTTs. Cutoffs at two standard deviations above the means were chosen because 22% of gravidas meeting those thresholds developed diabetes within 8 years.

In a subsequent publication, 17–23 years of follow-up determined that almost two-thirds had developed diabetes within that time period.⁶ The 1.9% prevalence of GDM identified by these cutoffs was similar to the 2% prevalence of diabetes in a nonpregnant population in the 1940s.⁷ If one standard deviation had been used as a cutoff, then 16% of pregnant women would have been diagnosed with GDM. O’Sullivan and Mahan expressed concern about the potential adverse psychological effect of overdiagnosis if the lower thresholds were applied and noted that the predictive value for future diabetes, using the recommended thresholds, was similar to the predictive value of a steroid-modified OGTT, which was in common use at the time.

O’Sullivan and Mahan decided to recommend that at least two values needed to be elevated in order to diagnose GDM, as was also the case for the United States Public Health Service (USPHS) criteria for diabetes in nonpregnant individuals. The authors stated “It was considered expedient... to require two or more values to be met or exceeded. In this way misclassification due to a laboratory error, or occasional single high peaks resulting from unusually rapid absorption of glucose, could be avoided.”⁸ It was thus determined that the 100 g, 3-hour OGTT would be used to diagnose GDM and that two or more elevated values would be required for this diagnosis. These two requirements have persisted in the United States well into the twenty-first century.

Although the O’Sullivan and Mahan criteria were accepted by the American College of Obstetricians and Gynecologists in the late 1970s,⁹ changes in laboratory methodology necessitated modification of the cutoffs, which were originally based on the Somogyi–Nelson method of measuring glucose, in venous whole blood samples, rounded to the nearest 5 mg/dL for easier memorization. In 1979, the National Diabetes Data Group (NDDG) in the United States recommended using the O’Sullivan criteria, modified to account for the use of plasma rather than whole blood by adding 15% to the already rounded values, then rounding again to the nearest 5 mg/dL.¹⁰ In 1982, Carpenter and Coustan published a second modification of the O’Sullivan and Mahan criteria, in which 5 mg/dL was subtracted from each of the original unrounded values, to account for the

Table 14.1 Various conversions of criteria for diagnosing gestational diabetes with 100 g, 3-hour oral glucose tolerance test

Test interval	O'Sullivan ⁶ mmol/L (mg/dL) ^a		National Diabetes Data Group ¹⁰ mmol/L (mg/dL) ^b	Carpenter/Coustan ¹¹ mmol/L (mg/dL) ^c
	Unrounded	Rounded		
Fasting	5.0 (90)	5.0 (90)	5.8 (105)	5.3 (95)
1 hour	9.2 (165)	9.2 (165)	10.6 (190)	10 (180)
2 hours	7.9 (143)	8.0 (145)	9.2 (165)	8.6 (155)
3 hours	7.1 (127)	7.0 (125)	8.0 (145)	7.8 (140)

Note: Two or more elevated values are needed for diagnosis.

^a Venous whole blood, Somogyi–Nelson technique.

^b Corrected for conversion from whole blood to plasma.

^c Corrected for conversion of whole blood to plasma and Somogyi–Nelson to enzymatic glucose measurement.

change from less specific Somogyi–Nelson methodology to more specific enzymatic glucose measurement, and the resulting values were increased by 14% because of the change from whole blood to plasma.¹¹ These various conversions of the original O'Sullivan and Mahan criteria are depicted in Table 14.1. When Sacks et al.¹² reconstructed the original methodology of O'Sullivan and Mahan and ran parallel samples of whole blood and plasma, using Somogyi–Nelson versus enzymatic methodology, only the Carpenter and Coustan conversions were within 95% confidence limits of the original O'Sullivan and Mahan values. By 2002, the American Diabetes Association (ADA) had endorsed the Carpenter and Coustan conversions.¹³

While the 100 g, 3-hour OGTT became the standard approach to diagnosing GDM in the United States, the 75 g, 2-hour OGTT was in wide use throughout the rest of the world. The World Health Organization (WHO) criteria for diagnosing diabetes and impaired glucose tolerance in nonpregnant individuals were commonly applied to pregnancy, such that if the fasting plasma glucose was below 7 mmol/L (126 mg/dL) and the 2-hour value (after a 75 g glucose challenge) was 7.8–11 mmol/L (140–199 mg/dL), GDM was diagnosed.¹⁴ A number of other tests and criteria are in use in various locations.

Another development in the United States was the use of a two-step protocol for screening and diagnosis of GDM. In 1973, O'Sullivan and colleagues described the glucose challenge test (GCT) based on data from 752 unselected gravidas who underwent the 50 g, 1-hour test and the 100 g, 3-hour OGTT.¹⁵ A whole blood, Somogyi–Nelson glucose of 7.2 mmol/L (130 mg/dL) was identified in 79% of individuals whose OGTT indicated GDM. This cutoff would be equivalent to 7.9 mmol/L (143 mg/dL) if plasma and an enzymatic method of analysis were used. A subsequent study¹⁶ demonstrated that a plasma glucose cutoff of 7.2 mmol/L (130 mg/dL), using an enzymatic method of glucose analysis, would identify nearly 100% of GDMs, while a 7.8 mmol/L (140 mg/dL) threshold identified 90% of cases. A recent systematic review of screening tests for GDM,¹⁷ performed for the U.S. Preventive Services Task Force, found that studies

evaluating a 7.8 mmol/L (140 mg/dL) threshold reported that 70%–88% of GDM cases would be identified, whereas a threshold of 7.2 mmol/L (130 mg/dL) identified 88%–99% of cases. At a threshold of 7.8 mmol/L (140 mg/dL), 11%–31% of unaffected gravidas would require an OGTT, while at 7.2 mmol/L (130 mg/dL), 23%–34% require further testing.

The need for new criteria

In 1991, the summary and recommendations of the *Third International Workshop-Conference on Gestational Diabetes*¹⁸ noted that there was a lack of international agreement on testing for GDM, with various countries and professional organizations promoting 50, 75, and 100 g glucose challenges as well as various sets of diagnostic thresholds. It was predicted that the 2-hour, 75 g OGTT eventually would become universally employed, just as it was for diagnosing diabetes outside of pregnancy. The report noted that none of the commonly used criteria were based on pregnancy outcomes. The summary pointed out that “With respect to GDM, the heart of the matter is the relationship between the degree of glucose intolerance and/or hyperglycemia and the risk of adverse maternal, fetal and neonatal outcomes...” The report concluded that “The highest priority should be given to efforts to develop international consensus on methods and definitions.” A 1992 international workshop sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) added further support to the need for carefully designed multinational studies to measure adverse perinatal effects of GDM.¹⁹

Hyperglycemia and Adverse Pregnancy Outcome study

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study²⁰ was based upon the rationale that overt diabetes clearly increases the risk of adverse pregnancy outcome, while controversy exists regarding the potential risk of

glucose intolerance during pregnancy less severe than overt diabetes. This blinded observational study of over 23,000 gravidas in 15 field centers in 9 different countries throughout the world was designed to determine the association between various levels of glycemia on a 2-hour, 75 g OGTT (performed between 24 and 32 weeks gestation) and adverse pregnancy outcomes. Primary outcomes included neonatal macrosomia (birth weight >90th percentile for the infant's sex, gestational age, race or ethnic group, field center, and maternal parity), primary cesarean section, clinical neonatal hypoglycemia, and cord blood C-peptide (a marker for fetal insulin level). Prespecified secondary outcomes included delivery before 37 weeks of gestation, shoulder dystocia or birth injury, the need for intensive neonatal care, hyperbilirubinemia, and preeclampsia. Figure 14.1 depicts the relationships between each of the three glucose tolerance test measurements and each of the four primary outcomes. Each relationship was significant but continuous, increasing from the lowest to highest glucose levels, with no obvious inflection point. Secondary outcomes were similarly continuously related to glucose tolerance test values, particularly with respect to shoulder dystocia/birth injury and preeclampsia. With the exception of clinical neonatal hypoglycemia (a rare outcome occurring in only 2.1% of cases), the relationships

held, with mild attenuation, when adjusted for multiple potential prespecified confounders, including maternal age, body mass index (BMI), smoking status, alcohol use, the presence or absence of a family history of diabetes, gestational age at the oral glucose tolerance test, sex of the infant, parity (0, 1, or ≥ 2 , except for primary cesarean deliveries), mean arterial pressure, and the presence or absence of hospitalization before delivery (except for preeclampsia), the presence or absence of a family history of hypertension, and maternal urinary tract infection (for analysis of preeclampsia only). Height was also included as a potential confounder, on the basis of post hoc findings of an association with birth weight greater than the 90th percentile. The three glucose tolerance test values were not highly cross-correlated and were independently predictive of adverse outcomes. The association between maternal glucose intolerance and macrosomia as well as cord C-peptide levels supports the 60-year-old Pedersen hypothesis that maternal hyperglycemia leads to fetal hypoglycemia, which in turn leads to fetal hyperinsulinemia and hence excessive fetal growth.²¹ A subsequent analysis of HAPO data²² demonstrated that neonatal adiposity was strongly correlated with both maternal OGTT values and cord C-peptide, lending further support to the aforementioned mechanism. Another analysis of

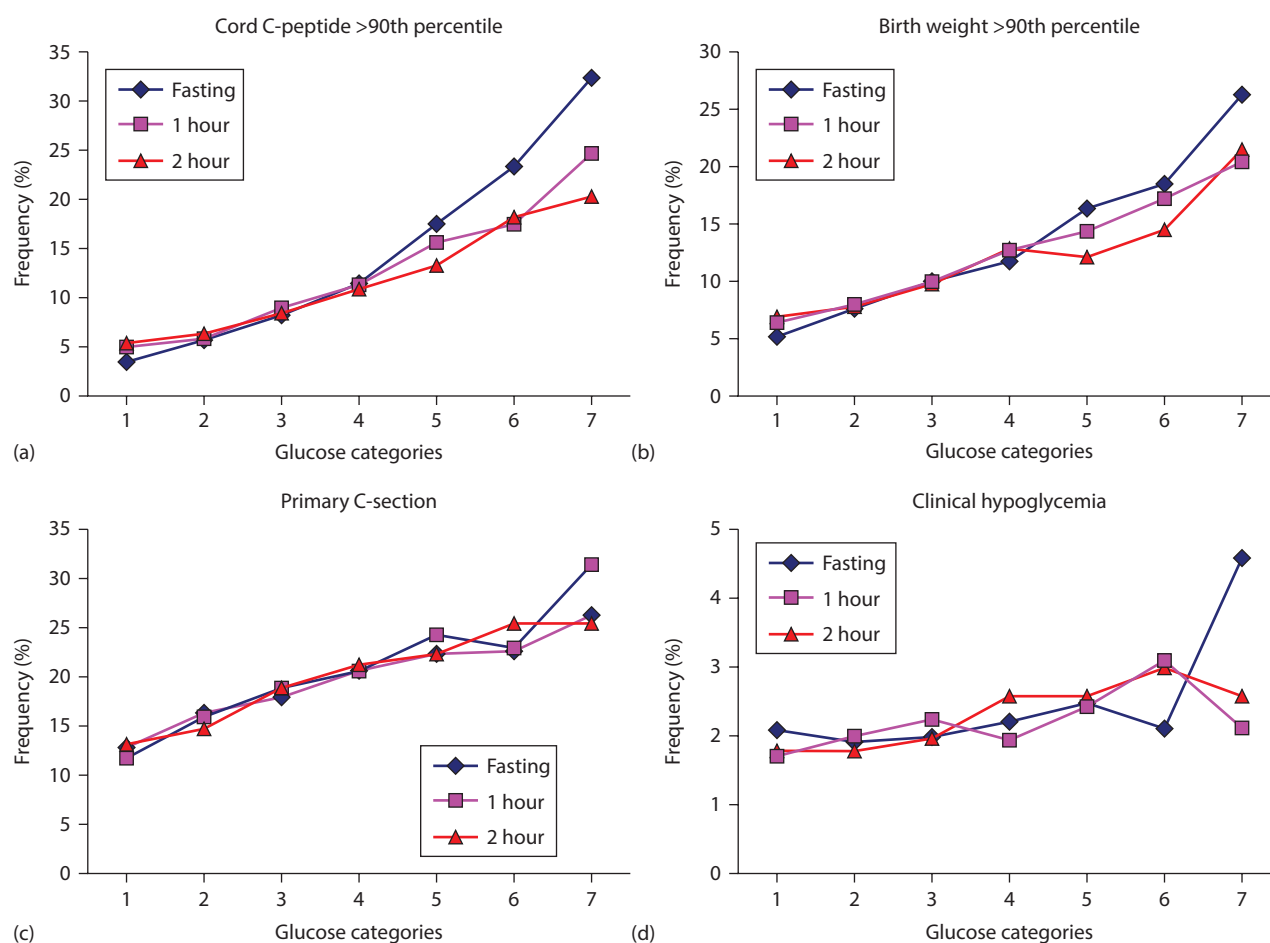


Figure 14.1 (a through d) Hyperglycemia and Adverse Pregnancy Outcome study: frequency of primary outcomes across glucose categories. (Reprinted from HAPO Study Cooperative Research Group, *N. Engl. J. Med.*, 358, 1991. Copyright 2008. With permission from Massachusetts Medical Society.)

HAPO data²³ revealed that maternal BMI and glycemia were independently predictive of adverse pregnancy outcomes, refuting the suggestion that GDM is simply a marker for maternal obesity.

International Association of Diabetes and Pregnancy Study Groups recommendations

Because there were no clear inflection points in the relationships between OGTT glucose values and the various adverse outcomes, the HAPO research group did not make any recommendations for GDM diagnostic criteria, preferring to leave such recommendations to a wider group of experts so as to foster better international ownership and acceptance. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) sponsored a *2008 Workshop-Conference on Gestational Diabetes Diagnosis and Classification* attended by more than 225 conferees from 40 countries. Published and unpublished HAPO results and other work on associations of maternal glycemia with perinatal and long-term outcomes in offspring were reviewed. A consensus panel of more than 50 individuals representing the member organizations of IADPSG and other groups carried out further review and analysis of HAPO results, held a second face-to-face meeting of panel members, and then published recommendations for the diagnosis and classification of hyperglycemia in pregnancy.²⁴

Results of a number of other epidemiological studies are consistent with the HAPO study findings indicating that associations between maternal glycemia and adverse outcomes are continuous across the range of glucose

concentrations below levels that are diagnostic of diabetes.^{25–29} However, because procedures for selection and enrollment of study participants, laboratory analyses, data collection, blinding study participants and caregivers to OGTT results, and analysis of results were all well standardized, HAPO study data were used by IADPSG as the basis to identify diagnostic thresholds for GDM.

Excess fetal growth, adiposity, and insulin secretion are integral features of diabetic fetopathy. The IADPSG-recommended diagnostic thresholds are the average glucose values at which odds ratios (ORs) for birth weight, cord C-peptide, and percent body fat, each >90th percentile, reached 1.75 times the estimated ORs of these outcomes at mean fasting, 1-hour, and 2-hour OGTT glucose values, based on fully adjusted logistic regression models. The resulting fasting, 1-hour, and 2-hour post 75 g glucose load thresholds are 92, 180, and 152 mg/dL, respectively (5.1, 10.0, 8.5 mmol/L). Risk ratios for the HAPO study outcomes in those defined as GDM compared with non-GDM are similar using glucose thresholds at ORs of 1.5, 1.75, or 2.0 relative to the mean glucose levels. Thus, in the final analysis, the choice of thresholds for associations that are continuous and linear is arbitrary.

Preexisting diabetes requires more intensive evaluation and treatment during early pregnancy. Because of the increasing prevalence of obesity and of diabetes in the general population and during pregnancy, the IADPSG also made recommendations for testing in early pregnancy to identify women with preexisting, untreated overt diabetes mellitus (Table 14.2).²⁴ The IADPSG panel concluded that there are insufficient data available to determine whether there was benefit to be derived from testing for GDM prior to 24–28 weeks gestation. Women diagnosed with diabetes or GDM during pregnancy should undergo postpartum glucose testing to detect persistent diabetes or prediabetes.

Table 14.2 International Association of Diabetes and Pregnancy Study Groups recommendations for detecting hyperglycemia in pregnancy

First prenatal visit

Measure fasting plasma glucose, A1c, or random plasma glucose on all gravidas or only high-risk gravidas:

- If diabetes (fasting plasma glucose [FPG] ≥ 7 mmol/L [126 mg/dL] or A1c $\geq 6.5\%$ or random glucose ≥ 11.1 mmol/L [200 mg/dL], confirmed by one of the other tests), treat as preexisting diabetes.
- If no diagnosis of diabetes and fasting plasma glucose ≥ 5.1 mmol/L (92 mg/dL) but <7.0 mmol/L (126 mg/dL), diagnose GDM.
- If no diagnosis of diabetes and fasting plasma glucose <5.1 mmol/L (92 mg/dL), test for GDM at 24–28 weeks.

24–28 weeks gestation

Perform 2-hour 75 g OGTT after overnight fast in women not previously diagnosed with diabetes or GDM earlier in pregnancy:

- Diabetes if fasting plasma glucose ≥ 7 mmol/L (126 mg/dL)
- GDM if one or more values equals or exceeds the following thresholds:
 - Fasting 7.0 mmol/L (92 mg/dL)
 - 1 hour 10 mmol/L (180 mg/dL)
 - 2 hour 7.9 mmol/L (143 mg/dL)
- Normal if all values below the above thresholds

Source: International Association of Diabetes and Pregnancy Study Groups Consensus Panel, *Diabetes Care*, 33, 676, 2010.

Case against adopting IADPSG recommendations

Since the IADPSG recommendations were published, there has been considerable controversy, with many authors expressing the view that they are unproven and it is not yet time for their universal adoption^{30–33} and others expressing opposing views.^{34–36} In the spring of 2013, the U.S. National Institutes of Health (NIH) convened a consensus panel to consider the available data and make recommendations.³⁷ The panel consisted of a number of individuals from various specialties who were considered unbiased, in that they have never published anything having to do with GDM. Experts in the field, on both sides of the issue being considered, presented available data for the panel to consider. In addition, a number of evidence reviews were conducted by the Agency for Healthcare Research and Quality. Recommendations from the consensus panel, which are not official recommendations of the NIH or any government agency, were published in the summer of 2013.³⁷ The panel acknowledged that there would be clear benefits to international standardization of the diagnostic approach to GDM. However, the panel opined that there is not sufficient evidence to adopt a one-step approach and recommended continuation of the current two-step approach for the time being. With regard to the two-step approach, the panel recommended that a single standard for the screening test cutoff and for the diagnostic thresholds be adopted by appropriate professional organizations. The rationale for the recommendation not to adopt the IADPS one-step approach can be summarized as follows:

1. The twofold to threefold increased frequency of the diagnosis of GDM that would result from adoption of the one-step approach will generate increased healthcare costs; it is not clear that this would be cost-effective.
2. It is not clear whether the additional women who would be diagnosed with milder GDM, and their offspring, would benefit from identification and treatment.
3. Labeling of these additional women may have unintended consequences, possibly including increased cesarean sections and adverse emotional impact on the mothers.
4. The variability inherent in the OGTT is known to be considerable; the use of a one-step process is likely to result in more “false-positives” than a two-step test.

Among its recommendations for future research, the panel suggested evaluation of the use of diagnostic thresholds based on ORs for adverse outcomes of 2.0 rather than 1.75 as recommended by IADPSG.

The case for implementing IADPSG recommendations

There is no question that the IADPSG recommendations offer numerous benefits, including but not limited to (1) the use of a uniform 75 g, 2-hour OGTT in all situations

rather than separate strategies for pregnant and non-pregnant individuals, (2) diagnostic criteria based on pregnancy outcomes, (3) comparability of data among the various regions of the world, and (4) simplification of the testing protocol and elimination of the dilemma surrounding the management of gravidas with a single elevated value on the 3-hour OGTT. In the paragraphs that follow, we shall deal with each of the concerns expressed by the consensus panel:

1. *Increased healthcare costs and lack of data on cost-effectiveness.* The IADPSG recommendations, when applied to the data in the HAPO study, identify 17.8% of participants as having GDM, when subjects unblinded because of GTT results above the unblinding criteria are included.³⁸ At the 15 field centers, rates of GDM varied from 9.3% to 25.5%. Although it is not currently possible to compare rates of GDM around the world because of the variability of diagnostic criteria, the International Diabetes Federation recently estimated that, based upon available data that were then adjusted to reflect the IADPSG criteria, the global prevalence of “hyperglycemia in pregnancy” is 16.9%, ranging from 10.4% in the North America and Caribbean region to 25% in the Southeast Asia region.³⁹ For comparison, rates of GDM (current criteria), based upon the 2008 hospital discharge data, from 23 states in the United States, ranged from 3.5% to 7.2%.⁴⁰ Hospital discharge data likely underestimate GDM rates due to incomplete testing of the population. Much of the difference among rates was attributable to differences in age, race/ethnicity, and insurance status. Institution of the IADPSG one-step approach would likely result in a twofold to threefold increase in GDM, although the increment might be more or less dramatic in particular locations. Thus, it is highly likely that healthcare costs will be increased. However, the current epidemic of obesity and diabetes is not limited to pregnant women; 4.5% of U.S. women aged 18–44 have diabetes⁴¹ and 26% have prediabetes.⁴² Since the IADPSG thresholds for GDM are not too different from the current diagnostic criteria for prediabetes, an 18% incidence of GDM does not represent over diagnosis. As diabetes has reached epidemic proportions throughout the world, we have not raised the diagnostic criteria to lower its prevalence; rather, healthcare providers and systems are attempting to meet the challenges posed. The same should be true for the “epidemic” of GDM; newer and more efficient ways to deliver care to these patients will need to be developed. One potential cost-efficient approach may utilize group prenatal counseling and care. It is not clear whether patients with milder forms of GDM will require the same intensity of antepartum fetal testing and monitoring as those with more severe GDM. Self-monitoring of blood glucose may be performed less frequently with mild GDM without adversely impacting on the time of initiation of treatment.⁴³ In two randomized trials of diagnosis and treatment of mild GDM, insulin was required in only 8%–20% of patients.^{44,45}

A recent cost-effectiveness analysis⁴⁶ compared the one-step IADPSG approach with the current two-step approach. It did not assume any increase in efficiency leading to decreased costs of care as outlined previously. The IADPSG approach was more expensive but was more effective in improving maternal and neonatal outcomes. In another study, the one-step approach was more cost-effective but only if women with GDM received postpartum testing and counseling to prevent the subsequent development of diabetes.⁴⁷ This finding highlights the opportunity for improvement in maternal long-term health that is presented by the diagnosis of GDM. While pregnancy outcome is the focus of efforts to test for GDM, there is additional benefit if future diabetes can be prevented. In a subset analysis of data from the Diabetes Prevention Program, subjects with previous GDM and current prediabetes who were randomized to intensive lifestyle intervention or metformin treatment developed type 2 diabetes at an approximate rate of 7.5% per year, compared to 15% per year in those randomized to the placebo arm of the study.⁴⁸ The numbers needed to treat with metformin or lifestyle change to prevent one case of diabetes over 3 years were 6 and 5, respectively. The diagnosis of GDM offers an important opportunity to dampen the epidemic of diabetes.

2. *Will identification and treatment of mild GDM provide benefit?* Two large randomized trials of identification and treatment of mild GDM were completed around the time of the IADPSG recommendations and have relevance to the aforementioned question. The Maternal-Fetal Medicine Units Network (MFMU) Network study⁴⁵ recruited women whose 50 g, 1-hour GCT was 7.5–11 mmol/L (135–199 mg/dL) to undergo a blinded OGTT. The 958 subjects with mild GDM (Carpenter and Coustan criteria with two or more elevated values but fasting plasma glucose <5.3 mmol/L [95 mg/dL]) were randomized to identification and treatment versus blinded OGTT results and standard prenatal care. The latter group also included a number of women with all OGTT results normal to ensure blinding of the caregivers. Identification and treatment of mild GDM resulted in reductions in preeclampsia, macrosomia, and shoulder dystocia of 50% or more, as well as a 20% reduction in cesarean sections. The Australian Carbohydrate Intolerance Study of Pregnant Women (ACHOIS) trial⁴⁴ enrolled gravidas who had risk factors for GDM or who had a 50 g GCT of 7.8 mmol/L (140 mg/dL) or greater to undergo a blinded 75 g, 2-hour OGTT. Subjects who had GDM, defined as a 2-hour plasma glucose of 7.8–11.0 mmol/L (140–199 mg/dL) and fasting plasma glucose below 7.8 mmol/L (140 mg/dL), were then randomized to identification and treatment of GDM or continued blinding of subjects and caregivers and routine prenatal care. Treated GDMs had a significantly lower incidence (1% vs. 4%) of the composite outcome (perinatal death, shoulder dystocia, bone fracture, or nerve palsy). In addition, identification and treatment of GDM was associated with significantly lower birth weight and rates

of LGA >90th percentile (13% vs. 22%), macrosomia >4 kg (10% vs. 21%), and maternal preeclampsia (12% vs. 18%). It should be noted that the GDM 2-hour OGTT diagnostic criterion of 7.8–11 mmol/L (140–199 mg/dL) is lower than the IADPSG recommended 2-hour criterion of 8.5 mmol/L (153 mg/dL). While the upper limit of fasting plasma glucose in ACHOIS was 7.8 mmol/L (140 mg/dL), the average fasting plasma glucose of ACHOIS subjects was 4.8 mmol/L (86 mg/dL). ACHOIS demonstrated benefit to identifying and treating GDM at diagnostic thresholds even lower than the IADPSG recommendations. In sum, there is evidence that identification and treatment of mild GDM is worthwhile.

3. *Will labeling of additional patients with GDM have adverse consequences?* The NIH consensus panel³⁷ noted studies demonstrating negative emotional impact of screening and diagnosis of GDM. However, when the ACHOIS RCT investigators measured emotional well-being of subjects and controls at 3 months postpartum,⁴⁴ women diagnosed and treated for GDM did significantly better than those in the control group who received routine pregnancy care. In another study, women with the diagnosis of GDM, including those who required insulin, manifested no difference in psychological status when compared to nondiabetic controls.⁴⁹ An apparent effect of labeling a patient with GDM was demonstrated in the Toronto Tri-Hospital Study,⁵⁰ in which identification and treatment of GDM (NDDG criteria) resulted in a relative normalization of macrosomia rates but a persistent increase in the cesarean rate compared to individuals with normal glucose tolerance; cesarean deliveries were not related to fetal macrosomia. An intermediate group with mild GDM (Carpenter and Coustan criteria), whose caregivers were blinded to the OGTT results, demonstrated an increased rate of both macrosomia and cesarean section, with cesareans being related to macrosomic babies. These findings suggest that obstetricians caring for the patients with known GDM were more likely to intervene despite the treatment being successful in preventing macrosomia, presumably because of concern over shoulder dystocia when GDM was present. These findings are in contrast to those of the MFMU Network trial⁴⁵ in which diagnosis and treatment of mild GDM resulted in a significant reduction in primary cesareans. Overall the evidence is mixed regarding unintended adverse consequences of diagnosing GDM.
4. *Will the inherent variability of the OGTT increase the rate of false-positive diagnoses of GDM?* The NIH consensus panel report³⁷ noted that the results of OGTTs “may differ in as many as 25% of women if performed at different times.” It is true that OGTTs are known to manifest variability; this is true for both pregnant and nonpregnant populations. However, the 75 g, 2-hour OGTT is the standard method of diagnosis of diabetes throughout the world despite its instability. While the two-step approach introduces two OGTTs, with the second (diagnostic) test presumably uncovering any false-positive result from the

screening test, the same is not true for a false-negative screening test. The systematic review cited earlier in this chapter¹⁷ reported that with a 50 g, 1-hour GCT cutoff of 7.8 mmol/L (140 mg/dL), approximately 10% of GDMs would be missed, when compared to a cutoff of 7.2 mmol/L (130 mg/dL). A similar result was reported in two earlier studies^{16,51} not included in the systematic review. Thus, the two-step process leads to both false-positives and false-negatives, and the false-negative results remain undetected. If our goal is to minimize the diagnosis of GDM, this approach would make sense. However, if our goal is to identify as many patients with GDM as possible so as to maximize the chance of preventing adverse outcomes, then the two-step process is not optimal. In contrast, the IADPSG-recommended one-step process produces no false-negatives or false-positives, since the 75 g, 2-hour OGTT is a diagnostic test and no screening test is involved. It could be argued that the diagnosis of GDM is really a “screening test” for adverse pregnancy outcomes, but if that were the case, then every GDM who does not have an adverse outcome would be termed a “false-positive,” whether diagnosed with the one-step or the two-step procedure. Such an argument defies logic, since there is no “disease” in which all diagnosed individuals suffer the same end results.

Finally, the suggestion that ORs of 2.0 be evaluated for GDM cutoffs, rather than the 1.75 utilized by IADPSG, misses the point that the 1.75 ORs referred to the comparison of adverse outcomes in gravidas for whom one or more glucose values exceeded the proposed thresholds to individuals at the mean for each of the three glucose measurements. When individuals in HAPO who met the IADPSG thresholds were compared with all individuals who had no glucose values exceeding thresholds, the likelihood of adverse outcomes was generally doubled or more (Table 14.3).

Current status

As noted earlier, the IADPSG recommendations were published in 2010.²⁴ In 2011, the ADA endorsed a modified version of the IADPSG recommendations.⁵² In 2013, the NIH consensus panel in the United States made its recommendation to maintain the status quo of the two-step, 100 g, 2-hour OGTT,³⁷ and in the summer of 2013, WHO recommended the one-step IADPSG approach⁵³ and noted that the number needed to screen to prevent one case of preeclampsia was

Table 14.3 Rates of adverse outcomes in Hyperglycemia and Adverse Pregnancy Outcome subjects without and with gestational diabetes mellitus by International Association of Diabetes and Pregnancy Study Groups criteria

	Normal glucose tolerance ^a (%)	GDM ^b (%)
LGA (birth weight >90th percentile)	8.3	16.2
Fetal hyperinsulinemia (cord C-peptide >90th percentile)	6.7	17.5
Neonatal adiposity (percent body fat >90th percentile)	8.5	16.6
Preeclampsia	4.5	9.1
Shoulder dystocia/birth injury	1.3	1.8

Source: Based on International Association of Diabetes and Pregnancy Study Groups Consensus Panel, *Diabetes Care*, 33, 676, 2010.

^a All three 2-hour, 75 g OGTT values below IADPSG threshold values.

^b IADPSG proposed criteria. All differences significant at $p < 0.01$ or better.

257 with this approach and to prevent one LGA baby was 117; both of these were fewer than the number needed to screen with the previous WHO criteria. At around the same time, ACOG confirmed its support for the two-step approach,⁵⁴ and in early 2015, the ADA revised its 2011 recommendation for the one-step approach and declared that either method is acceptable, but stating that the one-step approach may be preferable.⁵⁵ The Endocrine Society endorsed the IADPSG criteria and approach in 2013.⁵⁶ In 2015 the International Federation of Gynecology and Obstetrics endorsed the IADPSG one-step approach.⁵⁷ As of the writing of this chapter, there is not agreement in the United States as to which diagnostic approach is preferable. Around the world, various countries and professional organizations are debating which diagnostic criteria to adopt. It is to be hoped that in the not-too-distant future more evidence will be available to determine the costs, benefits, and risks of the IADPSG recommendations and that there will ultimately be universal agreement on how to diagnose GDM, similar to the agreement on the diagnosis of diabetes outside of pregnancy.

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15 Cost-effectiveness of screening and management programs for gestational diabetes mellitus

Louise K. Weile, James G. Kahn, Elliot Marseille, and Nicolai Lohse

Introduction

Whether gestational diabetes mellitus (GDM) screening and management by different criteria and in different settings is cost-effective has been debated for more than a decade. A 2009 report from *The Lancet's* Stillbirth Series steering committee put detection and management of GDM on a priority list of interventions to reduce stillbirth,¹ and the potential key role of GDM on the long-term health of the mother and her offspring is being discussed at the highest political level in the United Nations (UN) General Assembly and other UN bodies.²⁻⁴ The suggestion of new screening criteria by the International Association of Diabetes and Pregnancy Study Groups (IADPSG)⁵ in 2010 has added to the debate. These extensive deliberations notwithstanding, we are only beginning to understand which interventions might be effective at reducing the burden of GDM, and at what cost.⁶ To institute appropriate policies, decision makers at national and global levels need additional reliable information on the cost and cost-effectiveness of GDM screening and treatment.

This chapter aims to equip the reader with the conceptual tools and substantive background needed to understand and evaluate cost-effectiveness assessments of GDM and the implications of global policy from a health economic perspective. We start by a short background section. We then introduce and explain basic concepts of health economics as they relate to this issue, including resources and cost, health metrics, and different types of health economic evaluations. We review the current health economic evaluations on GDM screening and management, while elaborating these concepts. Finally, we provide a brief summary of cost-effectiveness results and discuss future directions for research.

Background

Current diagnostic and therapeutic recommendations for GDM are founded on the growing body of evidence of the *short-term* risks associated with GDM. For the offspring,

these include up to a 3.5-fold higher risk of macrosomia⁷⁻¹⁰ and elevated risk of shoulder dystocia and hypoglycemia.⁷⁻⁸ For the women, these include increased risk of cesarean section, polyhydramnios, gestational hypertension, and preeclampsia.⁷⁻¹² The recently published IADPSG diagnostic criteria,⁵ which are based on data from a large multicenter and multinational prospective study,⁷ are lower than some commonly used diagnostic criteria¹³⁻¹⁶ and therefore lead to a two- to threefold higher prevalence of GDM.^{17,18} The increase in GDM risk factors and the changed diagnostic criteria are both pushing GDM prevalence upward. The World Health Organization very recently approved the IADPSG criteria.¹⁹

Less visible are the *long-term risks* that potentially have a much larger effect on population health. GDM is increasingly mentioned as a possible contributor to the type 2 diabetes mellitus (T2DM) epidemic.²⁰⁻²³ Women with GDM have a more than sevenfold increased risk of T2DM (pooled relative risk = 7.43),²⁴ with cumulative incidence up to 70% in 3 years in some populations.²⁵ The risk of T2DM is most pronounced for women with high glucose values at the diagnostic OGTT during pregnancy or postpartum continuation of glucose intolerance,²⁶ greater body mass index, use of insulin during pregnancy (as a marker of severity of GDM), and earlier gestational age at diagnosis of GDM.²⁷ The offspring of mothers with hyperglycemia during pregnancy also carry an increased risk of prediabetes and T2DM later in life, four to eight times that of offspring born to mothers with normal glucose tolerance during pregnancy,^{28,29} with a 20-year cumulative incidence of up to 21%.²⁹ A modeling study from Canada estimated GDM as a forerunner of as many as 30% of T2DM cases in a high-prevalence diabetes population.^{30,31} This link between GDM and the *long-term health* of the pregnant woman and her offspring has only recently come to the attention of the GDM community.

GDM and T2DM share risk factors such as obesity and other metabolic disturbances, and the two epidemics are likely to move in tandem.^{4,32-34} Since the prevalence of GDM is increasing globally, identifying and providing

Table 15.1 Key types of cost-effectiveness analysis in health

	Definition	Outcome metric	Use to decide what?
Cost-effectiveness analysis	Net cost per added unit of health	ICER (i.e., cost/T2DM case averted or cost/brachial plexus injury averted)	What's the incremental cost per added health benefit? Is it worth doing versus a threshold?
Cost-effectiveness analysis (CUA)—with a standardized health metric	Net cost per added standardized unit of health (a ratio)	ICER (net costs/QALY gained or DALY averted)	What's the incremental cost per added QALY or averted DALY? Is it worth doing versus a threshold?
Cost-benefit analysis	Cost of intervention minus savings (a difference, not a ratio)	Net costs (benefits–costs) Typically includes benefits beyond health	Does the program produce more value than it costs? Is it worth doing?

Abbreviations: DALY, disability-adjusted life year, a measure of disease burden that sums premature mortality (LY) plus disabling morbidity (DA); ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year, a measure of health that tallies years alive adjusted for health status of those years.

good care for women with GDM could have substantial impact on population health in both high- and low-income countries.

Basic health economic theory

The benchmark of health economics is that resources such as labor, supplies, facilities, and equipment are scarce. The use of resources must therefore be based on priority. The focus of many economic evaluations both within the healthcare sector and elsewhere is on whether the commitments of resources in one area yield as good a return as would have been obtained if resources were committed elsewhere. An essential component in any such analysis is the *marginal cost*, understood as the cost of producing one additional unit of output such as a unit of health benefit. Costs and consequences are the input and output, respectively, of given health interventions. Drummond et al. define economic evaluation as “(...) the comparative analysis of alternative courses of action in terms of both their costs and consequences.”³⁵ Economic evaluations therefore aim at identifying, measuring, valuing, and comparing the costs and consequences of certain health alternatives. Thus, economic evaluations offer input for decision makers once issues of efficacy, effectiveness, and availability are settled.³⁵

Evaluation types

Only so-called full analyses can address the question of cost-effectiveness. Cost-effectiveness analysis (CEA), comprising cost-utility analysis (CUA), and cost-benefit analysis (CBA) are full analyses, because they compare costs and consequences between two and more alternatives. Partial analyses focus solely on costs or consequences, or they neglect comparison between alternatives. CEAs, CUAs, and CBAs assess

costs in monetary units, whereas they differ in the assessment of the consequences (Table 15.1).³⁵

Cost-effectiveness and cost-utility analysis

Within a GDM screening context, the outcome of a CEA could be *found cases of GDM* or *prevented cases of neonatal morbidity* depending on the time horizon used. As seen, the former outcome focuses on the effectiveness of screening, whereas the latter gives the opportunity of incorporating both effectiveness of GDM screening and management. However, both outcomes are specific to GDM and the obstetric field, and using these outcomes will narrow the scope of the economic evaluation. For decision making, these CEAs can only be used for comparison within an obstetric budget, which limits their use for broader priority setting.

A specific type of CEA combines both mortality and morbidity effects into one standardized single metric of change in health. This metric is either “disability-adjusted life years” (DALYs) or “quality-adjusted life years” (QALYs). DALYs measure the disease burden as it both represents premature mortality and disability due to morbidity.³⁶ Imagine an individual who would normally expect to live another 10 years. He is now diagnosed with T2DM and T2DM-related complications that give him a 10% disability compromise while alive, and he dies 8 years later. He will have a DALY burden of 2 (lost life years) + 0.1 (disability) * 8 (years living with that disability) = 2.8 DALYs. The QALY is a measure of health and essentially the negative of the DALY. Thus, an illness that shortens life by 2 years and lowers “health status utility” by 10% for 8 years would decrease QALYs by 2.8. Since QALY incorporates the utility of different health states into the outcome measure, analyses using this outcome are often classified as *cost-utility analysis*.

A CEA compares two different health interventions and expresses the net cost with the units of health benefit gained in ratio form, for example, as the “net cost per death averted”

or the “net cost per QALY gained.” This ratio is called the “incremental cost-effectiveness ratio” (ICER), because both the costs and health benefits are incremental.³⁵ Thus, the ICER expresses the additional cost incurred to gain one incremental health unit. The ICER has no useful meaning when programs result in net savings as there is no trade-off between costs and benefits. Instead, such intervention is classified as “dominant” (both cheaper and better) and as such should be a “no brainer” to health planners. Conventionally, the absolute magnitude of savings and health gains, with no ratio, is then reported.³⁶

DALYs and QALYs are generic health metrics and therefore not restricted to a certain health field. Thus, analyses using one of these metrics are often sufficient for decision makers comparing interventions broadly within the health-care sector.

Cost-benefit analysis

Though the concept of “cost-benefit” is frequently used as a layman’s term, CBA is actually a rarely used type of analysis in healthcare. The power of CBA is that it permits comparisons of widely disparate funding alternatives. In the CBA framework, the value of spending on sewerage work could be compared with spending on a maternal and neonatal health initiative. Hence, in CBA, all health outcomes including human life are assigned a monetary value,³⁶ i.e., the value of longer life and lower morbidity due to T2DM or other GDM-associated complications might be expressed as the sum of medical costs averted and economic productivity added compared with the cost of delivering GDM screening and management.

Due to the use of a monetary outcome, CBA enables general priority setting within all sectors, and this is a large part of its power and appeal. However, the monetary valuation of health outcomes often places great demand on data and analytic technique. Furthermore, placing a value on human health raises ethical issues, and for these reasons, CBA is rarely used in the evaluation of clinical or public health programs.³⁶

Designing health economic evaluations

Health economic evaluations typically combine *patient-level data* with *decision analytic modeling*. Use of patient-specific cost and consequence data, often obtained from clinical trials, may increase the precision of the analysis, but the results may not be applicable outside of the trial setting. Clinical trials measure *efficacy*, whereas the economic evaluation wants to estimate the *effectiveness* of a health intervention. Thus, using data collected with strict inclusion criteria will reduce the external validity of the economic evaluation. An economic evaluation of GDM screening and management based on data from a clinical trial will have difficulties estimating the effect on persons outside of the trial, and the often short duration of clinical trials may impede the very important estimation of long-term cost-effectiveness.

Decision analytic modeling allows all relevant alternatives to be taken into account, and intermediary outcomes

can be linked to endpoints by extending the time horizon. These models are suitable for decision making under uncertainty, and they also allow effectiveness to be estimated on multiple empirical studies. In the latter case, inclusion of studies should be based on a systematic literature search and include potential weighing and pooling of the studies. Decision models are often structured as decision trees or Markov models that can both be classified as cohort models. Decision trees represent the possible prognosis of an individual with or without an intervention. Events can be linked to costs and consequences, whereby the expected values of course of action within the competing alternatives can be calculated.³⁵

Confronting uncertainty

The models constructed to calculate cost-effectiveness are only representations of the factors that determine costs and consequences and of the way those factors interact. The usefulness of a model is therefore limited by the fidelity with which it represents the underlying reality. Fidelity in turn depends importantly on the accuracy and precision of the estimates of the models’ input values such as disease prevalence, the cost of screening, or the effectiveness of the interventions being evaluated. An integral part of almost any economic evaluation is therefore the systematic and transparent portrayal of the level of uncertainty and the confidence that should therefore be placed in the outputs of the model. The rigorous assessment of the magnitude and effects of uncertainty consists of a set of techniques known as “sensitivity analyses” since they quantify how “sensitive” results are to changes in input values or in the way those inputs interact. Sensitivity analyses should not be considered an optional feature of CEAs, but rather an essential part of the analysis, without which it is perilous to draw any conclusions.

Figure 15.1 represents a set of so-called one-way sensitivity analyses arrayed in a “tornado diagram.” It shows the effect on the outcome, in this case the cost-effectiveness of GDM screening in Chennai, India,³⁷ of an array of model inputs. The input with the greatest influence is at the top, and each successively less important one is stacked beneath it. The input with the greatest influence on cost-effectiveness is the cost of postpartum care. At 50%–150% of the \$2846 base case value, the ICER ranges from \$887 to \$2385 per DALY averted. These are called “one-way” sensitivity analyses because they show the effect of changing one input at a time, holding all of the other inputs constant. Other sensitivity analyses techniques can document the effect of simultaneously varying two, three, or more variables, including stochastic variations.

Costing methods

Costs are traditionally classified as direct, indirect, or intangible costs, but these can also be classified according to context: consumed within the healthcare sector and other sectors, by patients or relatives, or if a loss of production is seen. In order to take account of inflation due to different timing of the costs, these are typically valued after a given currency from a

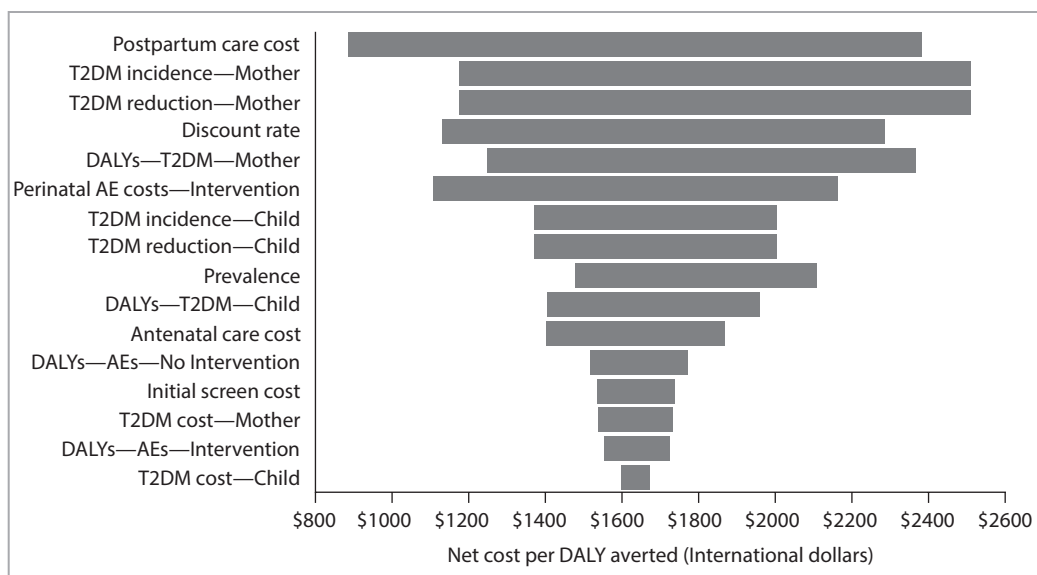


Figure 15.1 Sensitivity analyses arrayed in a tornado diagram. (From Marseille, E. et al., *J. Matern. Fetal. Neonatal Med.*, 26(8), 802, 2013. With permission.)

certain price year. Sources and methods for cost valuation are essential for the validity of the costing. As the health market is flawed by several attributes of the free market (i.e., third-party payment, regulations, and monopolies), costs should optimally be valued as the marginal cost—understood as the value of those benefits that cannot be gained if the resource is not available.³⁵ However, the concept of marginal costs will not be further elaborated in this chapter.

Discounting is based on the existence of “time preference” that is a preference of having resources *now* as opposed to *later* from the assumption that one can benefit from them in the interim. Both costs and consequences can be discounted according to a chosen discount rate per year. Discounting is a standard technique, but is sometimes considered controversial.³⁵ In relation to GDM screening and management, for example, discounting future saved costs and health gains of the offspring will imply inequality between mothers and offspring.

Comprehensiveness and scope

A comprehensive assessment of cost-effectiveness relies on inclusion of all relevant health program alternatives, meaning that a no-intervention alternative is essential if the full relevant range of options are to be assessed. The scope of an analysis is defined by the perspective (of the patient, healthcare system, or society) and the applied time horizon. Ideally, a societal perspective and lifelong horizon should be applied, and there must be consistency between stated perspective, time horizon, and the design of the analysis and included data.³⁵

Review of current literature on GDM cost-effectiveness

The following review includes all health economic evaluations published from 2002 to 2014.^{37–48}

In total, 12 publications were identified. Over time, the published evaluations moved from analyses of measured patient outcomes to decision analytic modeling, which allowed long-term outcomes to be considered. Furthermore, the most recently published decision models were more sophisticated, including input values and model design (Table 15.2).

Main findings

In general, large variations in the reported cost-effectiveness were identified. It was therefore impossible to draw broad conclusions about the cost-effectiveness of GDM screening from this dataset. First, many of the results (Table 15.3) were derived from one study,³⁸ which used natural outcomes such as “averted cases of perinatal mortality” or “averted cases of hypertension disorder.” In these analyses, total costs were divided by each of the outcomes separately, thus preventing an assessment of the cost of the combined results. Second, even where broad measures such as QALYs gained or DALYs averted were used, ICERs were calculated against different comparators and included different beneficiaries (i.e., some women only, some offspring only, and some both). Finally, one study³⁷ included averted cases of T2DM in both women and their offspring. This required the estimation of both the cost of postnatal interventions to avert T2DM and the discounted future benefits of averted case of T2DM. Since averted T2DM is a potentially large component of the benefit of GDM screening, studies that do not take these into account cannot be compared directly with those that do. Few assessments have compared IADPSG criteria to other accepted screening criteria, and results point toward the IADPSG criteria being cost-effective, but with great variations between studies.⁴⁹

The heterogeneity of the cost-effectiveness ratios could partly be explained by the different methods for calculation.

Table 15.2 Identification, measurement, and valuation of cost and consequences

Study	Key cost components	Cost sources/data handling	Consequence sources/data handling	Key input for decision modeling
Poncet et al. ³⁸	Screening tests Obstetrical care Management of GDM Delivery care Sick leave	Prospective study ($n = 120$) Hospital in Rhône-Alpes, France French key-letter costing system ($\approx$ DRG), literature, and expert opinions Discounting (NS)	Clinical effectiveness: published literature Decision modeling Discounting (NS)	GDM prevalence Screening refusal rate Risk factors Test effectiveness GDM treatment success
Larijani et al. ³⁹	Test materials Time for testing (staff)	Source for cost valuation (NS) Discounting (NS)	Clinical effectiveness: cohort ($n = 2416$), four university hospitals in Teheran, Iran, period or retro-/prospective design: NS Prevalence estimate on patient-level data Discounting (NS)	
Nicholson et al. ⁴⁰	Treatment of maternal/neonatal complications (direct and indirect costs)	The 2003 Medicare resource-based relative value units/The Maryland HealthCare Commission Database/The Bureau of Labor Statistics Market prices adjusted using <i>cost-to-charge ratios</i> Inflated into 2003 US\$ using consumer price index Discounted at 3% rate per year	Clinical effectiveness and utilities: published literature Life expectancy: the National Center for Health Statistics Decision modeling Discounting at 3% rate per year	GDM prevalence Test effectiveness Hypertensive disease Polyhydramnios Cesarean/vaginal delivery and associated complications Neonatal hypoglycemia Macrosomia Shoulder dystocia Morbidity/infant death
Ayach et al. ⁴¹	Laboratory costs (ND)	Public reimbursements Discounting (NS)	Clinical effectiveness: prospective cohort ($n = 341$) in university hospital in Mato Grosso do Sul, Brazil, July 1997–December 1999 Prevalence estimate on patient-level data Discounting (NS)	

(Continued)

Table 15.2 (Continued) Identification, measurement, and valuation of cost and consequences

Study	Key cost components	Cost sources/data handling	Consequence sources/data handling	Key input for decision modeling
Thung et al. ⁴²	Identified costs (ND)	Units/quantity/sources (NS)	Clinical effectiveness, lifetime expectancy, and utilities (NS)	Perinatal death Shoulder dystocia
NCCWCH (United Kingdom) ⁴³	Testing (ND) Treatment of GDM (staff's time, materials, medicine) Treatment of GDM-associated complications (ND)	Discounting (NS)	Decision modeling Discounting (NS)	Test effectiveness/acceptability GDM treatment Induction of labor/cesarean section Stillbirth/neonatal death Shoulder dystocia Bone fracture Nerve palsy Jaundice Hypoglycemia
		National Health Service/literature Inflated into 2006 U.K. pounds using retail price index Discounting (NS)	Clinical effectiveness and utilities: published literature Lifetime expectancy (NS) Decision modeling Discounting (NS)	
Lee et al. ⁴⁴	Treatment of GDM Treatment long-term child complications Preeclampsia management	Units/quantity/sources (NS) Discounting (NS)	Clinical effectiveness: published literature Lifetime expectancy and utilities (NS) Decision modeling Discounting (NS)	Maternal death due to preeclampsia Permanent brachial plexus injury
Meltzer et al. ⁴⁵	Test materials Time (staff/women)	Statistics Canada/Canada Revenue Agency Inflated into 2002 Canadian \$ Discounting (NS)	Clinical effectiveness: RCT ($n = 1594$) in university hospital in Montreal, Quebec, Canada, January 2001–2002 Prevalence estimate on patient-level data Discounting (NS)	
Round et al. ⁴⁶	Test materials Time for testing (staff) Treatment of GDM Treatment of GDM-associated complications	Literature/National Health Service data Inflated to 2009 U.K. pounds Discounting at 3.5% rate per year	Clinical effectiveness and utilities: published literature Lifetime expectancy: 80 years (reference NS) Decision modeling Discounted at 3.5% rate per year	Test effectiveness/acceptability GDM treatment Preeclampsia Induction of labor/cesarean section Neonatal jaundice Admission to neonatal nursery

(Continued)

Table 15.2 (Continued) Identification, measurement, and valuation of cost and consequences

Study	Key cost components	Cost sources/data handling	Consequence sources/data handling	Key input for decision modeling
Mission et al. ⁴⁷	Treatment/diagnosis of GDM (direct and indirect costs) Admission for GDM-related conditions omitted	Published literature Inflated into 2012 US\$ using consumer price index Discounting (NS)	Clinical effectiveness, utilities, lifetime expectancy: published literature Decision modeling Discounting at 3% rate per year	Test effectiveness GDM treatment Preeclampsia Mode of delivery Shoulder dystocia Macrosomia Brachial plexus injury Hypoglycemia Hyperbilirubinemia NICU admission Maternal/neonatal death
Werner et al. ⁴⁸	Testing (ND) Prenatal care Treatment of GDM-associated complications (short and long term) Prevention of GDM	Published literature/ Medicare reimbursements Inflated into 2011 US\$ using consumer price index Discounting at 3% rate per year (sensitivity analyses: 1%–5% rate per year)	Clinical effectiveness, utilities and lifetime expectancy: published literature Decision modeling Discounting at 3% rate per year (sensitivity analyses: 1%–5% rate per year)	Test effectiveness Preeclampsia Shoulder dystocia Preterm birth Cesarean delivery Stillbirth NICU admission Maternal diabetes postpartum
Marseille et al. ³⁷	Testing (materials, staff) GDM treatment and intervention Treatment of T2DM	Personal communications/ published literature Converted into 2011 International \$ Discounting at 3% rate per year	Clinical effectiveness and utilities: published literature Lifetime expectancy: country-specific WHO life tables from 2009 Decision modeling Discounting at 3% rate per year	GDM prevalence Test performance Effectiveness of treatment Full set of perinatal adverse events Maternal/offspring T2DM

Source: Weile, L.K. et al., *Best Pract. Res. Clin. Obstet. Gynaecol.*, 29(2), 206, 2015.

Abbreviations: DRG, diagnosis-related group; GDM, gestational diabetes mellitus; ND, not defined; NS, not stated; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

It was questionable whether the separately calculated ICERs performed in two studies^{38,40} clinically made sense. As the screening alternatives found most cost-effective in both these studies, it did not differ within strata. As the two studies^{44,47} did not include a no-screening alternative, the possibility of the alternatives in these evaluations actually not being cost-effective compared with no-screening could not be excluded. One-step 2-hour 75 g OGTT and two-step 1-hour 50 g

GCT $\pm$ 100 g OGTT were most frequently found to be cost-effective. However, it was questionable if the studies including these two screening types were comparable, as not only the criteria used for diagnosis but also the definition of the screened population varied widely among the evaluations. Thus, some studies relied on universal screening, whereas others relied on selected screening. Furthermore, within the selective screening options, different definitions of risk

Table 15.3 Estimates of cost-effectiveness

Study ^a	Screening alternatives	Reference	Incremental cost	Incremental cost (2014 US\$)	Per	Comment
Poncet et al. ³⁸	Two-step 1-hour 50 g OGTT ±100 g 3-hour OGTT, on high-risk pregnant women	No screening	€21,069.52	40,331	Averted case of macrosomia	
			€9,953.24	19,055	Averted case of prematurity	
			€7,871.55	15,071	Averted case of perinatal mortality	
			€28,674.90	54,898	Averted case of hypertension disorder	
	Two-step 1-hour 50 g OGTT ±100 g 3-hour OGTT, universal screening		€23,135.36	44,292	Averted case of macrosomia	
			€10,965.20	20,992	Averted case of prematurity	
			€8,663.83	16,587	Averted case of perinatal mortality	
			€31,898.74	61,070	Averted case of hypertension disorder	
	One-step 2-hour 75 g OGTT, universal screening		€68,933.79	13,1974	Averted case of macrosomia	
			€37,320.89	71,451	Averted case of prematurity	
			€29,444.16	56,370	Averted case of perinatal mortality	
			€94,506.04	18,0931	Averted case of hypertension disorder	
Nicholson et al. ⁴⁰	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	Referent			QALYs saved	Maternal consequences considered
	One-step 3-hour 100 g OGTT	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	US\$32,374	41,147		
	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	Referent				Neonatal consequences considered
	One-step 3-hour 100 g OGTT	Two-step 1-hour 50 g GCT ±3-hour 100 OGTT	US\$8,252	10,488		

(Continued)

Table 15.3 (Continued) Estimates of cost-effectiveness

Study ^a	Screening alternatives	Reference	Incremental cost	Incremental cost (2014 US\$)	Per	Comment
Thung et al. ⁴²	Two-step 1-hour 50 g GCT (BG > 7.8 1 hour), ±3-hour 100 g OGTT	No screening	US\$12,269	14,232	QALYs gained	
	Two-step 1-hour 50 g GCT (BG >7.2 1 hour), ±3-hour 100 g OGTT	Two-step 1-hour 50 g GCT (BG > 7.8 1 hour), ±3-hour 100 g OGTT	US\$14,961	17,355		
NCCWCH (United Kingdom) ⁴³	One-step 2-hour 75 g OGTT + ADA risk criteria ^a	No screening	UK£3,677	5,843	QALYs gained	
	One-step 2-hour 75 g OGTT + high-risk ethnicity	One-step 2-hour 75 g OGTT + ADA risk criteria ^b	UK£21,738	34,543		
Lee et al. ⁴⁴	One-step 2-hour 75 g OGTT (BG > 7.8 mmol/L 2 hour)	Referent			QALYs gained	
	One-step 2-hour 75 g OGTT (BG >7.0 mmol/L 2 hour)	One-step 2-hour 75 g OGTT (BG >7.8 2 hour)	US\$76,000	85,804		
Round et al. ⁴⁶	No screening	Distribution of the most cost- effective screening alternative	Maximum willingness to pay threshold at UK£20,000	Maximum willingness to pay threshold at US\$34,063	QALYs gained	Woman's individual risk of GDM <1%
	Two-step FBG ±2-hour 75 g OGTT					Woman's individual risk of GDM 1.0%–4.2%
	One-step 2-hour 75 g OGTT					Woman's individual risk of GDM >4.2%
Mission et al. ⁴⁷	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	Referent			QALYs gained	
	One-step 2-hour 75 g OGTT	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	US\$61,503	62,672		

(Continued)

Table 15.3 (Continued) Estimates of cost-effectiveness

Study ^a	Screening alternatives	Reference	Incremental cost	Incremental cost (2014 US\$)	Per	Comment
Werner et al. ⁴⁸	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	No screening	US\$543,119	564,844	QALYs gained	If diagnosis provides no long-term maternal health benefit
	Two-step FBG ±2-hour 75 g OGTT	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	US\$564,407	586,983		
	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	No screening	US\$16,689	17,351		
	Two-step FBG ±2-hour 75 g OGTT	Two-step 1-hour 50 g GCT ±3-hour 100 g OGTT	US\$20,336	21,149		
Marseille et al. ³⁷	One-step 2-hour 75 g OGTT	No screening	International \$1,626	580	Averted DALY	India
			International \$1,830	2,070		Israel

Source: Weile, L.K. et al., *Best Pract. Res. Clin. Obstet. Gynaecol.*, 29(2), 206, 2015.

Abbreviations: BMI, body mass index; DALY, disability-adjusted life years; QALY, quality-adjusted life years; 1-hour 50 g GCT, 1-hour 50 g glucose challenge test; 2-hour 75 g OGTT, 2-hour 75 g oral glucose tolerance test; 3-hour 100 g OGTT, 3-hour 100 g oral glucose tolerance test.

^a Results from studies not performing incremental analyses were excluded in the synthesis of cost-effectiveness estimates.

^b ADA risk criteria: American Diabetes Association definition of risk is having more of the following risk factors: >25 years, BMI > 27 kg/m²; family history of diabetes, and high-risk ethnic group.

factors were identified. As these small variations might have a significant clinical effect, none of the evaluations could be said to compare the same combination of alternatives. Thus, no summary conclusions could be made on these findings.⁴⁹

Future directions for health policies and health economic evaluations

As stated earlier, making general assessments of the cost-effectiveness of GDM screening and management based on the current evidence is difficult. We recommend that future research addressing this topic from a health economic perspective focus on national or regional policy alternatives instead of global conditions: a relevant assessment at least includes the national or regional existing screening program and screening alternatives that from a clinical perspective is judged worthy of recommendation. Currently, the screening program and criteria recommended by IADPSG therefore should be included as one alternative. Furthermore, a no-screening alternative should always be included, as this

supports a comprehensive review of feasible options and helps place other alternatives in context. Moreover, the potential of preventing effects on T2DM and other long-term complications for both mothers and their offspring should be incorporated in the analysis.

To produce results as relevant as possible to decision making, we encourage researchers to challenge their results by addressing ethical issues in the discussion of the results. If no screening is found to be the most cost-effective, is this actually a politically viable option within the relevant setting? Similarly, if the cost per health gain is high (i.e., poor cost-effectiveness), how will implementation of such alternatives affect other health initiatives depending on the same budget? As resources are scarce, priority is indispensable and trade-offs should be quantified. This is the heart of economic assessment and the main reason to perform CEAs. Hence, discussions of, for instance, whether GDM screening and management should take precedence over other interventions in pregnancy (i.e., screening for preeclampsia or general health promotion) are most needed. In theory, the discussion could even be expanded to compare GDM interventions with other nonobstetric

health interventions. The complexity of the full range of such possible comparisons is overwhelming. In practice, this complexity is greatly constrained by far smaller number of the actual policy-relevant choices facing political

and bureaucratic actors at any given time. By helping to guide us to options that yield high value for money, high-quality health economic evaluations can thus help address issues of broad importance to society.

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16 Changing health policy: From study to national policy

Ofra Kalter-Leibovici, Nicky Lieberman, Ronni Gamzu, and Moshe Hod

Background

Gestational diabetes mellitus (GDM) is associated with greater risk for immediate and late maternal and fetal adverse outcomes. Immediate adverse outcomes include fetal macrosomia, shoulder dystocia and birth injury, preeclampsia, and cesarean section.¹ Late adverse outcomes include greater maternal risk for type 2 diabetes mellitus (T2DM)^{1,2} and higher prevalence of childhood obesity and insulin resistance in offspring.^{3,4}

The risk of adverse outcomes in pregnancies complicated with GDM correlates with the level of maternal hyperglycemia,⁵ and interventions aimed to decrease hyperglycemia were reported to lower the risk of some of these outcomes (i.e., fetal macrosomia, shoulder dystocia, and preeclampsia).^{6–8}

Clinical guidelines advocate screening for GDM between 24 and 28 weeks of gestation, and most countries have designated screening programs that involve the testing of fasting and post-oral glucose load plasma glucose levels. In some countries, including Israel, a two-step screening program is employed, where pregnant women have 50 g oral glucose challenge test (OGCT), and those found with 1-hour postchallenge plasma glucose level of 140 mg/dL or higher have 3-hour 100 g oral glucose tolerance test (OGTT).⁹ The performance of OGCT has been recently evaluated in a systematic review of cohort studies. When GDM was diagnosed according to the Carpenter and Coustan criteria, a postload plasma glucose threshold of 140 mg/dL or higher provided 85% sensitivity and 86% specificity for GDM diagnosis, with positive and negative likelihood ratios of 5.9 and 0.18, respectively.¹⁰ Over the years, however, single- and two-step screening approaches have been proposed, using various oral glucose load doses and blood glucose thresholds for the diagnosis of GDM, with no consensus over a preferred method.¹¹ Furthermore, the fasting and postload plasma glucose thresholds used for diagnosis of GDM have been set according to the maternal risk of developing T2DM during follow-up, rather than the risk of immediate adverse pregnancy outcomes.¹²

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study addressed the ongoing debate on the best screening and diagnostic practices for GDM. The study

cohort included 25,505 pregnant women recruited at 15 centers in 9 countries. Two HAPO centers were located in Israel, including 3345 participants. All participants had a 2-hour 75 g OGTT between 24 and 32 weeks of gestation. Caregivers remained blinded with respect to the fasting and postload plasma glucose levels if these levels were 105 mg/dL or less and 200 mg/dL or less, respectively. Participants were followed till birth and information on maternal and fetal outcomes was collected. The study results showed a linear relationship between fasting and postload plasma glucose levels and adverse pregnancy outcomes, even in the range previously considered normal.¹³

The results of the HAPO study motivated the International Association of Diabetes and Pregnancy Study Group (IADPSG) to recommend universal screening for GDM with 2-hour 75 g glucose OGTT performed between 24 and 28 weeks of gestation. The IADPSG diagnostic criteria for GDM were determined according to the fasting and postload plasma glucose levels that were associated with odds ratios of 1.75 for having >90th percentiles of birth weight (large-for-gestational-age [LGA]), cord C-peptide, and neonatal percent body fat, as compared to the corresponding mean values of the entire HAPO cohort. The recommended plasma glucose thresholds are 92, 180, and 153 mg/dL for fasting, 1-hour, and 2-hour post oral glucose load state, respectively. A woman is diagnosed with GDM if she has at least one plasma glucose level equal to or higher than the threshold.¹⁴

Making local health policy

The IADPSG recommendation evoked international discussion as to whether GDM screening and diagnosis practices should be changed or not. The main concern raised was the need of healthcare systems to cope with a significant increase in the number of pregnancies previously considered normal that will now be classified and treated as GDM pregnancies, while there is no evidence from randomized trials showing that implementation of the new diagnostic criteria results in better pregnancy outcomes compared to those currently employed.¹⁵

We describe in this chapter the rationale and process of changing health policy of GDM screening and diagnosis in Israel, including the following steps:

1. Provision of locally relevant information for health policy decision making, based on the analysis of the Israeli HAPO study cohort data
2. Cost-effective assessment of implementation of the IADPSG recommendation, based on the data from Clalit Health Services (CHS), the largest health maintenance organization in Israel
3. Changing current health policy of GDM screening, diagnosis, and care in CHS

Step I: Data analysis

The analytical approach has been previously described.¹⁶ In brief, we compared the baseline characteristics and rates of pregnancy adverse outcomes in the Israeli HAPO study cohort ($n = 3,345$) and the rest of the HAPO study participants ($n = 19,971$). Based on the Israeli HAPO cohort data, we calculated the expected number of women diagnosed with GDM according to the IADPSG diagnostic criteria and compared this number with the number of women diagnosed with GDM in Israel, under the current two-step screening and diagnostic policy.

To estimate the expected yield of implementing the IADPSG recommendation, we calculated the number needed to screen (NNS) and the number needed to treat (NNT) to avoid one case of LGA or preeclampsia.

We developed a risk stratification tool for adverse pregnancy outcomes among IADPSG-positive cases.

We also explored two alternative screening strategies, either with fasting plasma glucose (FPG) or body mass index (BMI) and calculated FPG and BMI thresholds that provide a similar number of cases as the number of cases identified by the IADPSG criteria.

Finally, we explored a two-step screening approach, using FPG testing for the first step, and an OGTT with the IADPSG thresholds for the second step.

We found that the Israeli cohort significantly differed from the rest of the HAPO study cohort. Israeli participants were younger, less heavy, and more frequently multiparous and had lower FPG and postload plasma glucose levels. Adverse pregnancy outcomes were also less common in the Israeli HAPO cohort compared to the rest of the HAPO study cohort (Table 16.1). These findings emphasize the need to base health policy decisions, where possible, on local data. Nevertheless, the association between FPG and postload plasma glucose levels and the rate of adverse pregnancy outcomes were similar in the two HAPO groups.

Table 16.1 Comparisons of baseline characteristics and pregnancy outcomes between Israeli and other Hyperglycemia and Adverse Pregnancy Outcomes study participants

	HAPO study participants		P
	Israeli <i>n</i> = 3,345	Others <i>n</i> = 19,971	
Age, years, mean (SD)	27.8 (5.4)	29.4 (6.0)	<0.001
BMI, kg/m ² , mean (SD)	26.9 (4.4)	27.8 (5.4)	<0.001
Current cigarette smoking, %	5.9	6.9	0.024
Any alcohol consumption, %	0.5	8.0	<0.001
Multiparous, %	60.6	51.1	<0.001
Fasting plasma glucose, mg/dL, mean (SD)	78.4 (6.7)	81.3 (7.1)	<0.001
1-hour post-oral glucose load, mg/dL, mean (SD)	124.5 (30.4)	135.7 (30.7)	<0.001
2-hour post-oral glucose load, mean (SD)	101.8 (21.7)	112.5 (23.6)	<0.001
Cumulative percent positive by threshold			<0.001
Fasting ≥ 92 mg/dL	2.8	8.3	
1-hour post-oral glucose load ≥ 180 mg/dL	6.9	14.0	
2-hour post-oral glucose load ≥ 153 mg/dL	8.3	16.1	
Unblinded ^a	9.0	17.8	
Fetal macrosomia, %	8.8	9.7	0.11
Preeclampsia/eclampsia, %	1.3	5.4	<0.001
Primary cesarean section, %	10.0	17.0	<0.001
Birth injury/shoulder dystocia, %	0.3	1.5	<0.001
Preterm delivery, %	5.3	7.2	<0.001
Admission to neonatal intensive care unit, %	7.0	8.1	0.034

^a Women with fasting plasma glucose > 105 mg/dL, plasma glucose at 2-hour post-oral glucose load >200 mg/dL, or a random plasma glucose level > 160 mg/dL. Information on the plasma glucose levels of these women was disclosed to their caregivers.

Currently, about 7500 women, 4.3% of pregnancies in Israel are diagnosed with GDM, annually.¹⁷ Following the implementation of the IADPSG recommendation, the number of women diagnosed with GDM will double, adding extra 8000 women each year. Similar results were reported in other populations. For example, the implementation of the IADPSG recommendation is expected to cause a two- to threefold increase in the number of women diagnosed with GDM in the United States.¹⁵ Such increases require reorganization of the prenatal services and assessment of extra resources needed. To meet these needs, we developed an LGA risk score, based on maternal height, parity, and BMI at the time of screening. Using this score, we identified a subgroup consisting of about one-third of women diagnosed with GDM according to the IADPSG criteria, who had a lower rate of LGA than the rest of the IADPSG-positive cohort (9.8% vs. 19.7%, respectively). The rate of LGA offspring in this subgroup was closer to the rate of LGA in the IADPSG-negative group (8.1%). This subgroup, considered to have mild GDM, would probably benefit from less intensive perinatal care setup, focusing mainly on healthy lifestyle advice. Thus, the implementation of the IADPSG recommendation with further risk stratification may promote efficient utilization of available healthcare resources and allow the healthcare system to cope with the excess number of women diagnosed with GDM under the new diagnostic criteria.

Among IADPSG-positive women in the Israeli cohort, the rates of LGA offspring and preeclampsia were 16.4% and 1.8%, respectively. According to Landon et al.,¹⁸ intensive treatment of mild GDM is associated with a mean reduction of 51% in the risk of LGA offspring and a mean reduction of 54% in the risk of preeclampsia. Thus, the NNS and NNT to avoid one case of LGA are 145 (95% CI: 90, 232) and 12 (95% CI: 7.5, 19), respectively. The corresponding numbers for maternal preeclampsia are 1242 (95% CI: 431, 3584) and 103 (36, 292). These numbers are well within the range for other interventions in obstetrics, e.g., magnesium treatment for prevention of eclampsia¹⁹ and for neuroprotection,^{20,21} or progesterone treatment for the prevention of premature birth.²²

To explore alternative screening methods for detecting women at high risk of adverse pregnancy outcomes, we calculated the BMI and FPG thresholds at 24–32 weeks of gestation providing rates of positive cases similar to the rate of positive cases defined by the IADPSG criteria. These thresholds (at 24–32 weeks of gestation) were 33.5 kg/m² for BMI and 89 mg/dL for FPG. Using these thresholds, screening with FPG or BMI produced similar rates of LGA cases, as did screening according to the IADPSG recommendations (18.8% for FPG $\geq$ 89 mg/dL, 17.3% for BMI $\geq$ 33.5 kg/m², and 16.4% for IADPSG-positive women). Similarly, screening with FPG or BMI will detect a similar or even greater proportion of pregnancies complicated with preeclampsia (2.2% and 4.3%, respectively), as compared to the screening with the IADPSG criteria (1.8%).

Maternal overweight is associated with increased risk for adverse pregnancy outcomes (e.g., fetal macrosomia, preeclampsia, cesarean section, and shoulder dystocia), irrespective of blood glucose levels.^{23,24} Interventions aimed at

reducing or preventing maternal obesity are associated with lower risk of fetal macrosomia and preeclampsia.²⁵ Thus, the assessment of maternal BMI and provision of effective lifestyle advice should be pursued regardless of the evaluation of maternal glucose metabolism.

Screening with FPG may be an attractive alternative to OGTT, especially in developing countries. Agarwal et al.²⁶ reported that screening with FPG $\geq$ 88 mg/dL has reasonably good performance in terms of sensitivity (85%), specificity (71%), and area under the curve (AUC) (0.88) when tested against the American Diabetes Association diagnostic criteria of GDM. FPG of $\geq$ 90 mg/dL was reported to have 80% sensitivity and 91% specificity, with likelihood ratios of positive and negative test results of 8.84 and 0.21, respectively, when compared to the IADPSG diagnostic criteria for GDM.²⁷ Screening with FPG using a threshold of 85 mg/dL was previously reported to be associated with better sensitivity and specificity as well as positive and negative predictive values compared to OGTT.²⁸

It should be noted, however, that FPG and IADPSG diagnostic criteria do not necessarily detect the same population of positive cases.

Screening with FPG exclusively can miss cases that may still have high risk of adverse pregnancy outcomes despite having lower levels of FPG. We therefore developed a risk score for LGA offspring for women who have FPG < 89 mg/dL. Using this risk score, we could identify a subgroup of the women with FPG < 89 mg/dL who have 17.5% risk for LGA offspring, similar to the rate in women with FPG $\geq$ 89 mg/dL (18.8%). To avoid missing these cases, a two-step screening for GDM may be offered; first, all women will have a FPG test. Women with FPG $\geq$ 89 mg/dL will be diagnosed with GDM. Women with FPG < 89 mg/dL, who have high LGA risk score (about 20% of the women with FPG < 89 mg/dL), will have OGTT and will be diagnosed with GDM according to the IADPSG criteria. This two-step screening approach reduces the risk of missing LGA cases while still avoiding OGTT in more than 80% of pregnant women.

Göbl et al.²⁹ recently reported a similar two-step screening approach, using the FPG threshold recommended by the IADPSG ($\geq$ 92 mg/dL) for first-step screening and OGTT for second-step screening among women with FPG < 92 mg/dL and high LGA risk score.

Step II: Cost-effectiveness assessment

Economic analysis of data from the Australian Carbohydrate Intolerance Study in Pregnant Women trial (ACHOIS) randomized trial showed that treatment of mild GDM is associated with incremental cost of \$27,503 per serious perinatal complication prevented and \$2,988 per discounted life year gained.³⁰ Altogether, the intervention was judged as highly cost-effective. However, the costs of screening and diagnosis were not included in the analysis.⁷

Data from randomized controlled trials on the effect of GDM treatment on the risk of long-term adverse maternal and offspring adverse outcomes are scarce. Although insulin treatment in women with GDM was associated with reduction

in perinatal mortality, it did not affect the risk of maternal T2DM after 16 years of follow-up.³¹ Similarly, active treatment of GDM was associated with lower rate of fetal macrosomia compared to routine care in the ACHOIS trial; treatment had no effect on offspring BMI at the age of 4–5 years.³²

The costs of one-step screening methods for GDM were studied in a Canadian randomized trial. The results showed that a two-step screening process (OGCT followed by OGTT in positive cases) was associated with lower costs compared to one-step screening.³³

Werner et al.³⁴ analyzed the cost-effectiveness of the proposed IADPSG criteria for GDM screening and diagnosis, using a decision tree model. The investigators found that a two-step screening for GDM (using FPG and OGTT for the first and second step, respectively), implementing the IADPSG recommended glucose thresholds, was cost-effective providing that post-delivery lifestyle intervention will reduce the incidence of T2DM in mothers.

Lohse et al.³⁵ developed a computer simulation model to assess the cost-effectiveness of GDM screening and lifestyle change to prevent T2DM. The model was used to assess the cost-effectiveness of one-step GDM screening with 2-hour 75 g OGTT compared to no screening, using disability-adjusted life years (DALYs) for effectiveness measure.³⁶ The investigators used CHS database for information on the prevalence of GDM and costs. The model assumed that 80% of the women will receive postnatal care, including lifestyle advice. The effect of the lifestyle intervention was assumed to decrease the relative risk for T2DM both in mothers and children by 40%, resulting in 4 cases of T2DM averted among mothers and 2 cases among children per 1000 women screened for GDM. The net incremental costs (in international dollars) compared to no screening was \$76,102 per 1,000 women screened. The cost per DALY averted was \$1830, and 95% of the DALYs averted were due to T2DM prevention. In sensitivity analyses, lower uptake of postpartum care (50% instead of 80%) would raise the cost per DALY averted to \$2895. Assuming lower effectiveness of lifestyle advice (20% instead of 40% relative risk reduction of T2DM) would increase the cost per DALY averted to \$7242. With no benefit in reducing T2DM, the cost per DALY averted rises to \$182,750.

It should be noted that the estimated proportion of pregnancies complicated with GDM in this analysis was 2.6%, which is significantly lower than the rate of GDM according to the IADPSG criteria reported for the two participating Israeli centers in the HAPO study.³⁷

Step III: Changing current health policy

In order to understand CHS decision to change the current policy, the reader should get acquainted with the Israeli health system and the basic concepts of CHS's policy.

According to the National Health Insurance Law enacted in 1995, all Israeli residents are insured by one of the four health plans, currently providing healthcare services to over eight million people. CHS, the largest health insurer in Israel, insures more than half of the total Israeli population, with

overrepresentation of ethnically diverse and underprivileged population subgroups. Although people can move from one health plan to another every 2 months, less than 1% chose to do so each year. The low attrition rate provides an incentive for the health plans to invest in preventive medicine and in disease management programs. CHS was one of the first health plans worldwide to develop and implement a designated diabetes prevention program for people with pre-diabetes. The Israeli healthcare system is almost completely computerized, using electronic medical records with alerts and reminder generator and embedded decision support systems, allowing data sharing between different providers.

CHS runs a comprehensive diabetes community program since 1997. Most people with diabetes are managed by their primary practitioners and other community healthcare providers, including nurses, pharmacists, dietitians, and physiotherapists. Patients are referred to consultant diabetes specialist in case of uncontrolled diabetes or severe diabetic complications. CHS developed its own diabetes practice guidelines, endorsing international standards, and being regularly reviewed and revised every 2–3 years. The diabetes disease management program within the primary care setup in CHS addresses also other comorbidities and risk factors that are associated with diabetes, e.g., hypertension, dyslipidemia, and cardiovascular disease. The comprehensive care provided is culturally sensitive, addressing the ethnic diversity of the insured population. As a result, more than 55% of people with diabetes have HbA1C level of less than 7%, and more than 70% have their HbA1c level within their personally adapted target; more than 60% of the diabetic patients have LDL cholesterol levels lower than 100 mg/dL, and more than 75% of the patients with diabetes have LDL cholesterol level of less than 130 mg/dL. As a result of the comprehensive diabetes care provided to people with diabetes, there has been a significant decline in the rate of nontraumatic amputations, invasive procedures for coronary reperfusion and blindness due to diabetic retinopathy. As a result, the costs of the person with diabetes decreased by about 40%, from the provider perspective.

Given the general policy that promote disease prevention, the high risk of T2DM in women with GDM, and the favorable result of the cost-benefit analysis, CHS decided to adopt the IADPSG recommendation and to adapt the care model according to the increased number of patients diagnosed with GDM.

CHS will adopt the risk-stratification approach described earlier, stratifying the women diagnosed with GDM according to the new diagnostic criteria into high-, intermediate-, and low-risk subgroups. Women considered being in the low-risk group will be provided with lifestyle advice, including dietary counseling and physical exercise, and follow-up by their primary practitioners and consultant gynecologists. Counseling will be provided by nurse educators, dietitians, and occasionally diabetes specialists. Healthcare for women in the intermediate-risk subgroup will be provided in community, Women Health Centers of CHS, by multidisciplinary teams, which consists of lifestyle advice and hypoglycemic drug therapy. High-risk patients will be referred to high-risk pregnancy units in the regional hospitals.

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17 Ideal weight gain in diabetic pregnancy

Gerard H.A. Visser and Harold W. de Valk

Introduction

Weight gain during pregnancy is related to pregnancy outcomes that include preterm delivery, fetal macrosomia, and intrauterine growth restriction. The former two are common in women with diabetes; the latter one has become rare with better care and lower incidence of vascular complications in these women.^{1,2} Optimal weight gain differs according to the maternal body mass index (BMI) and is lower in women with a high BMI. Weight loss during pregnancy is usually associated with an impaired outcome. In this chapter, optimal weight gain during pregnancy in women with diabetes is discussed.

Optimal weight gain

Most data on optimal weight gain concern the general pregnant population, with specific data on maternal diabetes generally lacking. Weight gain should especially be restricted in obese women, since excessive weight gain hampers an already impaired outcome. This has been nicely shown in a study in 481 obese glucose-tolerant women: a gestational weight gain of 5–10 kg was associated with a doubling of the incidence of maternal hypertensive disease, cesarean delivery, induction of labor, and large-for-gestational-age (LGA) infant as compared to a weight gain of less than 5 kg.³ In case of a weight gain of 10–15 kg and more than 15 kg, these risks were on average threefold and fourfold higher, respectively.

In 2009, new guidelines on optimal weight gain were published by the Institute of Medicine.⁴ These guidelines were developed

to minimize the negative health consequences for both mother and fetus of both inadequate or excessive gain. This was assessed primarily by considering the outcomes most consistently and plausibly associated with gestational weight gain: infants born either small- or large-for-gestational (SGA and LGA, respectively) age, the mother's risk for an unplanned cesarean delivery and excessive (>5 kg) postpartum weight retention.

The guidelines are shown in Table 17.1, according to prepregnancy BMI. In women with type 1 diabetes, it has recently been shown that weight gain above the recommended value, as defined before, may result in a striking increase in fetal macrosomia: 42% of LGA as compared to 8% in women with the recommended weight gain.⁵ In women with gestational diabetes mellitus (GDM), most of the weight gain occurs prior to GDM diagnosis (for references, see Most and Langer⁶). In a study in GDM, the lowest incidence of LGA occurred in normal weight women when weight gain was in accordance with the Institute of Medicine guidelines. In case of overweight (BMI 25–30) or obesity (BMI > 30), the lowest LGA incidence occurred in women with a lower weight gain than recommended in the guidelines (<8 and <4.5 kg, respectively).⁶

The guidelines on optimal weight gain do not contain subdivision according to the three obesity classes (I, BMI 30–35; II, 35–40; III, >40), since data were not sufficient to do so. However, in severely obese nondiabetic women with a BMI > 40, there is evidence that weight gain during pregnancy should be below 5 kg for an optimal outcome with a low preterm delivery rate.⁷ In a large study in 6500 obese women in California, it was found that the lowest risks for preterm birth, small for gestational age (SGA), and LGA occurred with a maternal weight gain of 9–13.5 kg in the Class I group, 5–9 kg in the Class II, and 2–5 kg in Class 3. In Class III, African-American women's best outcome occurred in the case of weight gain below 2 kg.⁷ In the case of weight loss, there was an increase in preterm delivery in all three obesity classes. A large German study also has shown that gestational weight loss was associated with an increase in preterm delivery and SGA, apart from obesity class III.⁸ The potential hazards of gestational weight loss should not be underestimated and weight loss cannot be recommended.⁹

Discussion

Fetal macrosomia in women with diabetes depends on many factors, such as genetics and epigenetics, prepregnancy BMI, glucose control during pregnancy, and

Table 17.1 Recommended weight gain in pregnancy according to the Institute of Medicine Guidelines

BMI	Recommended weight gain	
	kg	lb
<18.5	12–18	28–40
18.5–25	11.5–16	25–35
25–30	6.8–11.4	15–25
>30	5–9	11–20

Source: Rasmussen, K.M. et al., *Curr. Opin. Obstet. Gynecol.*, 21, 521, 2009.

gestational weight gain. Good glucose control in early pregnancy is associated with an increase in macrosomia, probably due to a better placentation, whereas a good control late in pregnancy decreases the risk (see Chapter 49). Disappointingly, many of these risk factors cannot be influenced although weight gain in pregnancy may be modifiable through dietary and behavioral interventions. However, even with intensive guidance, the results seem to be only moderate.^{10,11} A recent meta-analysis of randomized and nonrandomized clinical trials on dietary and lifestyle

interventions in overweight and women obese has shown a 2 kg lower maternal weight gain in the treatment arm with a trend toward a reduction in the prevalence of gestational diabetes.¹² There were no differences in the incidence of LGA infants. All studies were assessed as being of low to medium quality.

In women with preexisting diabetes or GDM, the incidence of fetal macrosomia is high, and macrosomia is one of the key factors important for childhood and later obesity and metabolic syndrome. Adequate counseling and dietary advices are, therefore, particularly important in these women. This is facilitated by the fact that these women will be frequently seen during pregnancy by a dedicated endocrinology/obstetrics team, with their weight be measured during each visit. In the second trimester of pregnancy, it appears possible to identify women at risk of gaining weight outside of the guidelines, which may facilitate dedicated action.¹³ However, in the case of GDM, most weight gain has already occurred before diagnosis. One study has indicated that optimal weight gain in overweight and obese women with GDM should be lower than that recommended for the general population. Weight gain in pregnancy should regularly be assessed, and in the case of weight gain below or above recommended values, appropriate dietary advices should be given.

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18 Medical nutritional therapy for gestational diabetes mellitus

Lois Jovanovic

Introduction

Pregnancy causes a multitude of metabolic changes within a woman's body in order to provide the proper nutrients to the developing fetus. In women with type 1 and type 2 diabetes and gestational diabetes mellitus (GDM), these metabolic perturbations must be treated distinctly and aggressively to optimize fetal development and health. Pregestational diabetes (either type 1 or type 2) has the potential to subject the developing fetus to abnormal maternal glucose levels resulting in problems with organogenesis producing congenital abnormalities or spontaneous abortion. Furthermore, GDM presents after organogenesis in the second part of pregnancy; therefore, the major risk for the fetus is macrosomia. Although the goal for dietary therapy for each of these disorders is the same, which is euglycemia, the means to achieve it are very different and somewhat controversial. In the case of GDM, the mainstay of therapy is medical nutritional therapy, whereas in insulin-requiring diabetes, dietary therapy is compensated with premeal insulin injections. In this chapter, the metabolic changes in normal pregnancy will be presented followed by the general guidelines for pregnancy. Fetal complications associated with inadequate nutrition or metabolic perturbation will be briefly explored, followed by issues and treatment for GDM, with emphasis on specific dietary therapies for GDM.

Metabolic changes in normal pregnancy

During pregnancy, metabolism increases by 15%–26% to support both the mother and developing fetus.¹ Early pregnancy is characterized by normal glucose tolerance, normal hepatic gluconeogenesis, and normal or improved insulin sensitivity.^{1–5} As pregnancy progresses, carbohydrate metabolism becomes altered due to an increase in insulin secretion and decreased insulin sensitivity. Thus, some insulin resistance occurs, by late pregnancy, overall insulin action is decreased 50%–70% as compared to nonpregnant

women.⁵ Lipid metabolism is also altered in hepatic and adipose tissue. Early-pregnancy hormones, estrogen, progesterone, and insulin, promote the storage of lipids within maternal tissues.

Therefore, in early pregnancy, initially there is a decrease in serum triacylglycerols, fatty acids, cholesterol, lipoproteins, and phospholipids. However, as estrogen and insulin resistance impacts the mother, lipolysis and hypertriglyceridemia ensues.⁵ For example, at week 12, estrogen causes cholesterol, specifically HDL, to be utilized as a major metabolic fuel for the placenta throughout the remaining weeks of pregnancy; thus serum concentrations increase. Furthermore, VLDL is altered in the second and third trimesters due to a change in adipose and hepatic enzyme activity, specifically the decrease of lipoprotein lipase (LPL). Notably, when maternal glucose levels decrease as can be seen during the fasting state, hepatic LPL activity increases allowing the mobilization of lipids and ketones for fetal nutrition. Human chorionic gonadotropin, prolactin, and glucagon also contribute by stimulating lipolysis in late pregnancy. This serves to preferentially send glucose and protein to the fetus, while the maternal tissues rely more on fatty acid oxidation and ketogenesis to meet their energy requirement. Finally, during the third trimester, a change in hepatic gluconeogenesis can be seen. Due to a 10–15 mg/dL decrease in the basal rate of glucose and an insulin concentration of two times the concentration seen in nonpregnant women, the liver must compensate by secreting 16%–30% more glucose to meet the energy needs of both the mother and fetus.^{3,6,7} Assel et al.⁷ found that the maternal hepatic glucose production is dependent upon the maternal body weight in a linear fashion. Late pregnancy also is characterized by a rise in the carbohydrate contribution to the overall oxidative metabolism as energy.

In normal pregnancy, metabolic changes occur to shunt nutrients from the mother to the fetus, allowing for optimal development and growth; however, as we explore the following sections of this chapter, it will become apparent that alteration based on input and dysfunction can alter the body's natural plan and cause distress to both the mother and fetus.

General nutritional guidelines for pregnancy

Normal pregnancy nutritional guidelines focus on several dietary elements. Major topics include caloric intake, macronutrient proportion, vitamins and minerals, and alcohol consumption. The energy requirements of the fetus must be met to ensure proper development and provide postpartum lactation without causing excessive maternal weight gain. The energy standard to support a pregnancy has been debated heavily and will be explored in the section "GDM and nutritional therapy." The American College of Obstetricians and Gynecologists advocates several basic concepts for a balanced diet for pregnant women. They suggest eating three to four servings of fruits and vegetables, nine servings of whole grains for energy, three servings of dairy for calcium, and three servings of meat to reach daily protein requirements. Vitamin supplementation to achieve daily nutrients, as an adjunct to a healthy diet, is encouraged when recommended by the woman's physician. Certain foods should be avoided in pregnancy due to fetal developmental harm. These include deli meat, certain preparations of smoked fish, soft cheeses, unpasteurized milk, refrigerated pate, raw meat, and raw eggs, which have been associated with bacterial infections such as *Salmonella*, *Listeria*, and *Escherichia coli*. *Toxoplasma gondii*, the protozoan that causes toxoplasmosis, has also been found as contaminant in unwashed vegetables and raw meat. Fish containing mercury and raw shellfish should be avoided. Caffeine has been associated with miscarriage, premature birth, low birth weight, and withdrawal symptoms in the neonate when consumed in large amounts in pregnancy. However, other studies have implicated caffeine intake in modest levels to be nondetrimental in pregnancy. Until further studies can evaluate the effects of caffeine, it is recommended to be avoided altogether.^{8,9} Alcohol should not be used in any amount during pregnancy. In utero exposure has been linked to developmental disorders such as fetal alcohol syndrome. Also, alcohol should be avoided postpartum while breast-feeding.¹⁰

GDM

As discussed in the previous section "Metabolic changes in normal pregnancy," the nondiabetic woman undergoes drastic and dynamic metabolic changes to provide glucose as the preferential energy source to the developing fetus. Although the pathophysiological mechanism behind GDM remains unknown, some current theories include a predisposition to future type 2 diabetes triggered by the changes in metabolism that normally accompany pregnancy or an increased response by the woman's body to normal metabolic changes of pregnancy. GDM has been defined as "glucose intolerance of variable severity with onset or first recognized during pregnancy."¹¹ It is important to note that GDM does not cause a malfunction in insulin secretion or improper proinsulin or glucagon activity: insulin resistance remains

the prominent characteristic.¹² In the United States, GDM affects 2%–14% of the pregnant population per year depending on the ethnicity of the population studied.^{13,14} A woman who is most likely to be affected by GDM is one who is obese, is >25 years of age, has a family history of diabetes especially in first-degree relatives, and has a past medical history for glucose intolerance or metabolism problems and/or miscarriages or other obstetric problems. Additionally, Latino, African, Native American, South or East Asian, and Pacific Islanders are at a higher risk for developing GDM.¹⁵ The Santa Barbara County Health Care Services Program Study¹⁶ found that women who meet several of these criteria, at the greatest risk, should be tested as early as feasible, while those with average risk should be tested at 24–28 weeks gestation. However, GDM can easily appear in low-risk women; therefore, universal screening would be ideal.

Screening methods for GDM

The screening methods for GDM are very controversial. The two sets of criteria endorsed by the World Health Organization (WHO) or the U.S. National Diabetes Data Group are each distinct and are primarily based on statistical standard deviations without regarding the level of clinical outcome achieved. An attempt to set international standards and identify those at risk for developing GDM is currently under way in a 5-year, prospective, observational, and multicenter study, the Hyperglycemia and Adverse Pregnancy Outcomes study. It involves 25,000 women in 10 countries and specifically will look at the clinical outcomes with respect to cesarean delivery, fetal hyperinsulinemia, macrosomia, and neonatal morbidity in correlation to maternal glycemic levels.¹⁷

Fetal complications of maternal hyperglycemia

Uncontrolled hyperglycemia primarily affects fetal growth on both extremes of the normal growth curve. In those diabetic mothers that have advanced vascular disease, fetal growth deceleration may occur due to placental insufficiency. Fetal growth deceleration is defined as those in lower fifth percentile on a growth curve adjusted for gestational age.^{18,19} Macrosomia is defined as an absolute birth weight of greater than 4000 g or greater than the 90th percentile (adjusted for gender, ethnicity, and gestational age). Cesarean sections often must be performed when the baby is at term to reduce the risk of birth trauma such as Erb's palsy or Klumpke's paralysis.²⁰ Cesarean sections also add risk to the mother's health. As explained by the Pederson hypothesis,²¹ the effects of an intrauterine environment of hyperglycemia and hyperinsulinemia include hypoglycemia, organ developmental problems (especially gastrointestinal), erythrocytosis, iron redistribution, calcium and magnesium deficiencies, respiratory problems (respiratory distress syndrome), cardiac problems (intraventricular hypertrophy and

cardiomyopathy or heart failure), hyperbilirubinemia, and neurological sequelae.

A multitude of metabolic problems occur that not only affect the immediate future of the neonate, but as these children mature, they are predisposed to future metabolic problems, such as type 2 diabetes and metabolic syndrome.^{22,23} Subsequently, this pattern of metabolic disease takes a cyclic course affecting future generations.

Does treatment of GDM make a difference in pregnancy outcome?

In June 2005, Crowther and colleagues²⁴ published the results of a 10-year multicenter randomized clinical trial in Australia and the United Kingdom called the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) (Table 18.1). The purpose of the ACHOIS was to determine whether medical nutritional therapy, glucose monitoring, and insulin therapy were superior to routine prenatal care with regard to reducing the risk of perinatal complications and postpartum maternal health status. A total of 1000 women participated in this trial, 490 in the intervention group and 510 in the routine care group with eligibility based upon the presence of one or more risk factors for GDM or a positive 50 g glucose challenge test (GCT) who did not have an indication of pregestational diabetes, history of GDM, or an active chronic disease. The WHO criteria were used to identify those with GDM, and women with severe glucose impairments were excluded. Therapies provided to the women in the interventional group consisted of dietary counseling with consideration to prepregnancy weight, activity level, normal dietary intake, and weight gain. Women were asked to self-monitor their glucose levels four times a day and proceed with insulin therapy dosage

adjustments based upon those levels. Women in the routine care group received care from blinded clinicians as to the status of the previously performed oral glucose tolerance test (OGTT). However, if the clinician felt the patient was experiencing glucose intolerance, assessment and treatment could be instituted at his or her discretion. Otherwise, prenatal care that was specific to the center visited was given. Primary outcomes included one or more perinatal complications defined as death, shoulder dystocia, bone fracture, and nerve palsy. Admission to the neonatal intensive care unit and jaundice that required phototherapy was also assessed. Secondary outcomes included a consideration of the primary outcome, gestational age at delivery, overall birth weight and birth weight adjusted for gestational age, and the presence of macrosomia or fetal decelerated growth. Maternal outcomes were assessed on the basis of general and mental health including depression, anxiety, gestational age at birth, mode of birth, weight gain during pregnancy, hospital admissions and prenatal visits, and common complications, such as pregnancy-induced hypertension. The ACHOIS study²⁴ established several significant results in both the neonatal and maternal outcomes. The rate of serious adverse perinatal outcomes was significantly different between the interventional and routine care groups at 1% versus 4%, respectively ($p < 0.01$). This rate established the number needed to treat at 34 to reduce the incidence of perinatal complication. Newborns in the interventional group were admitted to the neonatal intensive care units more often, at a rate of 71% versus 61% admission rate in the routine group ($p < 0.01$). No significant difference was seen when considering the length of stay in the NICU or use of phototherapy due to jaundice. The percentage of mothers who were induced into labor was 39% in the interventional group versus 29% in the routine care group ($p < 0.001$). However, rates and the reason for cesarean sections were similar between the groups.²⁴ With regard to the secondary outcomes, the interventional group neonates

Table 18.1 Summary of the Australian Carbohydrate Intolerance Study in Pregnant Women study

Maternal and neonate primary, secondary outcomes evaluated	Intervention group, $n = 490$ mothers, 506 neonates	Routine group, $n = 510$ mothers, 524 neonates
Perinatal complications ($p = 0.01$)	1%	4%
NICU admission rate ($p = 0.01$)	71%	61%
Length of stay and phototherapy implementation (NSD)	Median 1 day Interquartile range, 1–2 days	Median 1 day Interquartile range, 1–3 days
Labor induction ($p < 0.001$)	39%	29%
Rate of cesarean section (NSD)	31%	32%
Mean birth weight ($p < 0.001$)	3335 $\pm$ 551 g	3482 $\pm$ 660 g
Large for gestational age ($p < 0.001$)	13%	22%
Macrosomia ($p < 0.001$)	10%	21%
Small for gestational age (NSD)	7%	7%
Maternal Edinburgh postnatal depression Score > 12 ($p = 0.001$)	8%	17%

Source: Crowther, C.A. et al., *N. Engl. J. Med.*, 352, 2477, 2005.
Abbreviation: NSD, no significant difference.

had significantly lower mean birth weights ($p < 0.01$) and were born earlier presumably due to higher labor induction rates. However, when adjusting for gestational age with respect to birth weight, there were significantly fewer neonates born to interventional mothers that qualified in the large-for-gestational-age category. Additionally, macrosomia occurred significantly less often, but the rate of infants in the small-for-gestational-age group did not differ between the interventional and routine care groups. Maternal outcomes regarding maternal perception at 3 months postpartum of health showed an improved quality of life in the interventional mothers specifically with a reduction in the incidence depression, 8% versus 17% as measured by the Edinburgh Postnatal Depression Scale²⁴ (Table 18.1). The ACHOIS study clearly shows the benefits of using a multifaceted approach toward managing GDM to the neonate and the mother. Not only does it advocate dietary and insulin therapies, but also when one considers the population chosen and the method of randomization, it supports the use of universal screening. Based on the study design, the interventional group would be equivalent to universal screening practices and the routine group would represent those in which GDM screening is not routine. Therefore, by applying the results of the study in the women receiving routine care, only 34 women would need to be treated with interventional therapies to produce one improved neonatal outcome. Given the severity of an adverse neonatal outcome, this finding would support expanding the GDM screening population to include women who would routinely not be screened for GDM.

GDM and nutritional therapy

As demonstrated earlier, management of GDM is multifaceted. Insulin therapy, exercise, and diet are all vital components toward reducing the incidence of maternal hyperglycemia and ultimately fetal complications. The remainder of this chapter will focus on GDM nutritional therapy. Currently, there is no universally accepted medical nutritional therapy for the treatment of GDM. The American Dietetic Association advocates the standard medical nutritional therapy for a GDM mother to be the standard therapy advocated in nonpregnant adults with the carbohydrate content standard being $<60\%$ carbohydrate per meal. However, when these standards were followed, an increase in insulin therapy was seen in more than 50% of women with GDM.²⁵ Additional studies have supported lower carbohydrate percentages. For example, in a study involving obese women with GDM, when the carbohydrate was restricted to 33%, the infants were all within normal birth weight ranges and there was no evidence of maternal ketonemia.

Ketonemia and ketonuria

Following an overnight fast, 10%–20% of all pregnant women have ketones in their blood.^{26,27} This fasting ketonemia or “starvation ketonemia” has not been associated

to fetal detriment. However, in studies conducted by Rizzo and colleagues, hyperketonemia during pregnancy, which results from maternal diabetes (hyperglycemia), has been implicated to affect the fetus’s intellectual and behavioral development as measured by the Bayley Scales of Infant Development and the Stanford–Binet Intelligence Scale, which were administered at ages 2 and 3, 4, and 5 years, respectively. Hence, it was suggested that ketonemia be avoided in all pregnant women.²⁸ Buchanan and colleagues contrasted the metabolic response in normal pregnant women without GDM, to those who were obese with GDM. He subjected both groups to an overnight fast and then an extended 18-hour total fast. Obese women with GDM had a greater decrease in plasma glucose levels and were not more prone to develop ketonemia than the normal pregnant women. This result would support the use of decreasing the frequency of meals in order to achieve lower preprandial glucose levels in obese women with GDM.²⁹ In a study of type 1 diabetic women, Jovanović and coworkers showed that those infants whose mothers had the lowest betahydroxybutyrate levels had the largest infants because mothers’ postprandial glucose concentrations were higher due to the increased caloric intake prescribed to avoid the ketonemia.³⁰

Caloric restriction

Caloric restriction in pregnant women with GDM is another aspect of medical nutritional therapy that needs to be addressed. When women who are classified as obese or overweight prior to pregnancy, the amount of weight gain in pregnancy differs from those who are at a normal or underweight prior to pregnancy. The National Academy of Science has recommended that for women greater than 150% of ideal body weight, no more than 15 lb should be gained with pregnancy. Optimal infant birth weight was achieved when less than 3 kg or no weight was gained in these women.³¹ Hypocaloric diets have been explored in women with GDM based upon a 2400 kcal/day diet. Investigators³² compared a 2400 kcal/day diet to a 1200 kcal/day diet and achieved significant differences in average glucose and fasting insulin levels, but not in fasting or post-GCTs. Those in the 1200 kcal/day group developed ketonemia and ketonuria; therefore, the study was discontinued due to the controversial association of ketones with fetal developmental harm. Subsequently, in another study conducted by the same investigators, within the first week, when compared with the 2400 kcal/day diet, a 1600 kcal/day diet improved fasting and mean daily glucose values without the development of ketonemia. Further studies have advocated a 1500–1800 kcal/day diet for obese women with GDM with similar results.²⁶ The standards for energy requirements for pregnant women with GDM, as supported by the American College of Obstetrics and Gynecology, determine the amount of energy needed to maintain pregnancy based upon the pregravid weight. For women with GDM, who are 1.5 times their ideal body weight, the caloric intake is 12–15 kcal/kg of the current pregnant weight, while those at less than 0.8 of their ideal body weight are to increase their caloric intake to 35–40 kcal/kg current pregnant weight.

For those at 0.8–1.2 times their ideal body weight, 30 kcal/kg, and those at 1.2–1.5 times ideal body weight, 24 kcal/kg current pregnant weight is the standard.¹⁵ The “euglycemic diet” advocated the lower range of the spectrum set by the American College of Obstetrics and Gynecology.

Carbohydrate restriction

The Pederson hypothesis attributes fetal macrosomia due to hyperinsulinemia caused by maternal hyperglycemia. Several studies have shown that when maternal glucose levels are well controlled, the incidence of macrosomia, fetopathy, and cesarean sections decreases.^{21,33–35} Currently, there is no set standard for pre- and postprandial levels in women with GDM. Optimally, the therapeutic target of glucose levels in a woman with GDM would be the same as those who are pregnant without diabetes. Normoglycemia in the pregnant, nondiabetic, nonobese woman was demonstrated in studies conducted in 2001, by Parretti and colleagues.³⁴ In this study, the postprandial mean glucose during the third trimester did not exceed 105.2 mg/dL (5.8 ± 0.27 mmol/L). At 28 weeks gestation, the daily mean glucose levels was 71.9 ± 5.7 mg/dL, and at 38 weeks, it increased to 78.3 ± 5.4 mg/dL, which would coincide with the normal insulin intolerance increase, respectively. Parretti et al.³⁴ also accessed the clinical outcome of these pregnancies based on fetal growth. They found that 1-hour postprandial glucose levels at 28 weeks through the third trimester had a positive correlation to fetal abdominal growth. Furthermore, the results are supportive in attributing the postprandial 1-hour glucose levels as a predictor of infant birth weight, fetal macrosomia, fetal hyperinsulinemia, and fetal abdominal circumference in nondiabetic pregnancies. Therefore, one may consider the level of insulin resistance as a spectrum, in which those with GDM are affected in the same way as nondiabetic pregnant women but to a greater extent. Hence, the levels of glycemia achieved in nondiabetic pregnant women to decrease incidence of fetal complications and growth would be applicable to those with GDM. Another study to support the importance of postprandial glucose levels is the Diabetes in Early Pregnancy Study, which was conducted with type 1 diabetic mothers. When postprandial glucose levels increased, there was an increased risk of macrosomia. The threshold for the marked increase was seen when postprandial glucose levels reached 120 mg/dL.³⁵ Thus, a dietary therapy, “the euglycemic diet” was developed on the basis of this study.

The euglycemic diet takes into account the metabolic changes that occur within the pregnant woman as she goes throughout her day. In the morning, a surge of cortisol is seen (“the dawn phenomenon”), which causes the release of glucose from stored sources and hepatic gluconeogenesis; thus the blood glucose is higher to begin with. Therefore, a decreased amount of carbohydrate is needed in the breakfast meal. A small study ($n = 14$) was conducted in women with

GDM who have greater than 130% of their ideal body weight at 32–36 weeks’ gestation. The goal was to achieve a postprandial of 120 mg/dL at 1 hour. None of the patients were on an insulin regimen and a caloric restriction of 24 kcal/kg/day was established. Patients kept a diary of glucose levels taken four times a day and food intake. The carbohydrate parameters of the diet were as follows: 12.5% of the total daily carbohydrate at breakfast, 28% at lunch and dinner, with the remainder in three snacks disturbed throughout the day. The postprandial glucoses recorded by the women correlated to the carbohydrate intake. From this study, the author has adapted this diet to achieve optimal control of glycemic levels in her patients. Most women with GDM are very compliant and want to do what is necessary to have a healthy baby. By having patients take an active role in their medical care, they can significantly reduce their risk for fetal macrosomia. In a study conducted by de Veciana et al.³⁶ when patients monitored their pre- and postprandial glucose levels, the risk of fetal macrosomia decreased from 42% to 12%. Additionally, these patients also had lower hemoglobin A1c levels, therefore supporting that they maintained lower glycemic levels. Hemoglobin A1c is an effective clinical tool for accessing glycemic control and can be performed every 2 weeks to chart management because the turnover rate of the red blood cells during pregnancy is only 90 days as compared with 120 days in the nonpregnant state. Thus a significant improvement in glucose control is manifest by a significantly improved hemoglobin A1c level, although the steady state has not been achieved until after 6 weeks. Patients monitor their pre- and postprandial glucose levels and only proceed with a meal when their preprandial glucose levels are 90 mg/dL or less; otherwise, insulin is initiated. A preprandial glucose of 90 mg/dL and a postprandial of 120 mg/dL may seem controversial or strict; however, given the risk of macrosomia and the positive outcomes that have been obtained clinically, the authors of this chapter advocate these glycemic goals for medical nutritional therapy.³⁷

It is imperative that patients learn which foods have high carbohydrate content, so educational lessons and nutritional food label reading is essential for the success of any therapy that is instituted. Patients are given a list of recommended high-carbohydrate foods in order to remind them what needs to be portioned. For example, the “big 5” are potatoes, rice, pasta, bread/tortillas, and cereal (Figure 18.1). By teaching patients to adhere to a euglycemic diet, not only are they able to control their glucose levels effectively, but also they are able to modify their diet postpartum facilitating weight loss.

A simple teaching tool that is used in Santa Barbara County is shown in Figure 18.2. The one-page handout identifies the foods to avoid, foods to eat with caution, and foods that may be eaten that minimally impact postprandial glucose concentrations and thus can be eaten liberally. Ideally, a breakfast of less than 33% of the daily carbohydrate intake, lunch at 45%, and a dinner at 55% are suggested to maintain a postprandial glucose level of 120 mg/dL.³⁸

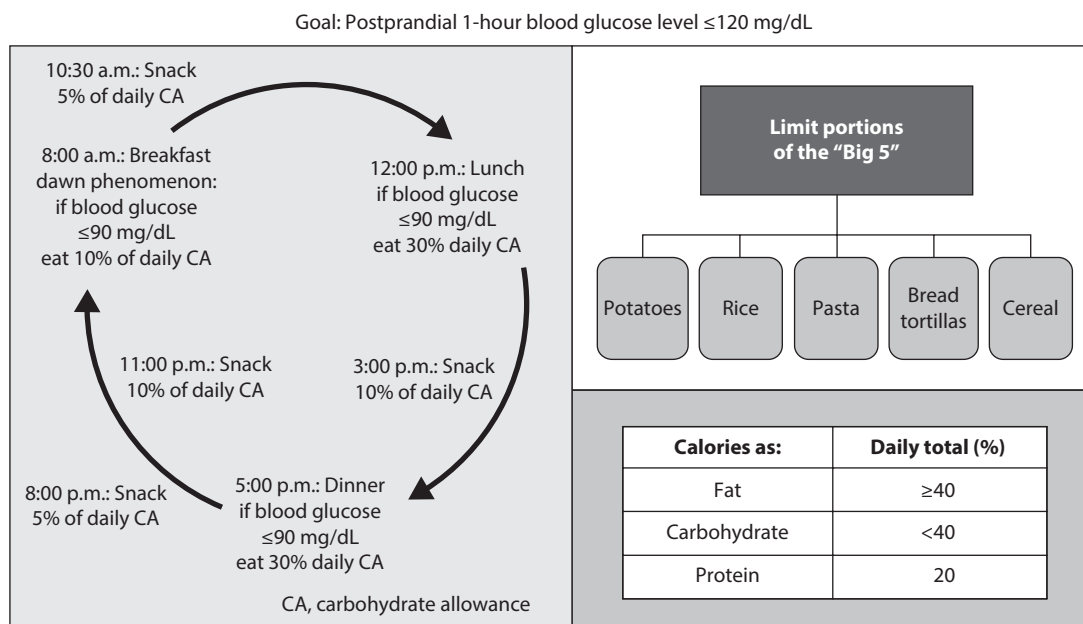


Figure 18.1 The euglycemic diet.

Role of fats in GDM therapy

Fat content in the American Diabetic Association's diet consists of less than 25% of the total caloric intake, whereas the euglycemic diet is composed of 40% of the total daily caloric intake. The role of saturated and monounsaturated fats in women with GDM is different with respect to the uptake of glucose postprandially. In a study comparing these two types of fats, 1-hour postprandial glucose levels are approximately equal; however, the duration of the elevated glucose levels differs. In women with GDM who consumed monounsaturated fat, the glucose levels remained elevated at a longer period of time, and thus insulin dosage had to be adjusted to counteract the maintained elevated glycemia. Conversely, meals consumed containing saturated fat had a shorter duration of elevated glucose levels, making them preferential with regard to glycemic control of postprandial glucose levels. Furthermore, lower postprandial durations decrease the risk of macrosomia and the need for increased insulin doses.³⁹ Advocating saturated fats over monounsaturated fats is understandably controversial due to the correlation that has been made with saturated fats and heart disease in nonpregnant individuals. Further studies are needed to answer whether eating a higher proportion of saturated fat during medical dietary therapy for GDM at approximately gestation weeks 24–40 is a significant time period to have adverse long-term effects on the mother versus the benefit of controlling postprandial glucose level duration, which decreases the risk of fetal complication.

Role of protein

Protein content in the American Diabetes Association (ADA) diet and euglycemic diet makes up 20% of the total

daily caloric intake. Increased satiety has also been correlated with meals that are high in protein content.^{40,41} Thus, this aspect could help morbidly obese patients manage their overall caloric intake especially when moderate caloric restriction therapy is being used. Low-carbohydrate/high-protein diets in normal pregnant women have been explored notably in the Motherwell studies running from 1938 to 1977. The Motherwell studies suggested a link between increased protein content and low birth weight.⁴² Recent studies have expanded the initial Motherwell studies by looking at the offspring of these studies as adults. It has been hypothesized that increased protein intake can stimulate maternal cortisol production and expose the fetus to high levels of cortisol which may facilitate lifelong hypersecretion of cortisol. Herrick and colleagues found a correlation to increased plasma cortisol levels consequently causing hypertension in the adult Motherwell offspring.⁴³ However, they postulated that the type of protein consumed and the type of carbohydrate paired with it may factor into the physiologic affects seen. Cofactors needed for protein metabolism such as folate and vitamin B6 may be excluded when certain types of carbohydrate are avoided, such as bread and potatoes and green leafy vegetables, as was done in the Motherwell studies.

"In mothers with a limited capacity to synthesize nonessential amino acids, maternal amino acid oxidation could impair fetal growth as a result of reduced availability of nonessential amino acids."⁴² Therefore, the physiologic effect of low birth weight on the fetus would be caused multifactorially and not just due to high protein consumption. Additional studies will be necessary to determine the role of high-protein diets in pregnant women and, specifically, in women with GDM.



Figure 18.2 The one-page handout used in Santa Barbara County.

Conclusion

GDM is a period of glucose intolerance that manifests at the beginning of the third trimester. Metabolic changes in the normal pregnant women also have a degree of insulin resistance that shunts glucose preferentially to the fetus. To maintain blood glucose levels within a tight range, the normal pregnant woman must increase her insulin secretion up to fourfold. When the pancreas is not able to compensate for the increased insulin needs of pregnancy, GDM occurs resulting in hyperglycemia and hyperinsulinemia in both the mother and fetus. These increased glucose and insulin levels manifest a multitude of fetal and maternal complications, the most prevalent being macrosomia. Other complications include hypoglycemia, erythrocytosis, hypocalcemia and hypomagnesemia, hyperbilirubinemia, iron redistribution, respiratory distress, and neurological effects. Poor gestational metabolic management can

be directly linked to the level of neurological functioning of the child, and these children are more prone to develop metabolic syndromes such as type 2 diabetes. This would affect generations to come as well. The management of GDM is based upon the synergistic effects of medical nutritional therapy, exercise, and an insulin regimen when necessary. Therefore, the identification and treatment of GDM is crucial. Screening tests using at-risk formulations and OGTTs remain a point of controversy. Universal screening would be optimal to identify those with GDM. The research clearly shows the benefit of expanding screening and providing medical nutritional therapy, glucose monitoring, and insulin therapy to all women who manifest even minor elevations of glycemia and thereby decrease perinatal complications, such as macrosomia. Maternal postpartum depression rates may also be improved with improved care during pregnancy. Multiple studies have correlated fetal complications such as macrosomia to 1-hour postprandial

glucose levels. By restricting carbohydrate concentration in the euglycemic diet and modifying the caloric intake based on pregravid weight, success has been achieved in reducing large-for-gestational-age and macrosomic infants. The euglycemic diet targets a preprandial glucose of 90 mg/dL or less and a 1-hour postprandial of 120 mg/dL. Optimal glucose levels have been heavily debated and there is not currently a universal standard. However, research has shown that normal pregnant women in the third trimester have lower preprandial and postprandial glucose concentrations than nonpregnant women. This would support advocating lower standards of ≤ 90 mg/dL preprandially and 120 mg/dL postprandially for women with GDM. Hypocaloric diets have been explored and appear safe for the obese woman with GDM. The American College of Obstetrics and Gynecology advocate consideration of the mother's pregravid weight when considering the caloric needs per kilogram per day. The presence of maternal ketonemia and ketonuria is controversial with respect to fetal development, and the mechanisms and outcomes associated with ketonemia resulting from uncontrolled glucose levels and starvation may be

different with respect to detriment to the fetus. Fat content also remains controversial although studies have shown that meals with saturated fat as compared to monounsaturated fat result in the same-hour postprandial glucose level, but the duration of the level is shorter facilitating lower insulin dosages. High-protein/low-carbohydrate diets are also controversial and in normal pregnant women have been correlated to lower birth weights and adult offspring increased cortisol levels. However, satiety is also important and protein malnutrition should be avoided in pregnancy. More research is necessary to determine the effect of these macromolecules on normal pregnant individuals and those with GDM. Overall, medical nutritional therapy is one of the staples of GDM management. Women with GDM are very compliant and most are willing to make dietary changes in their lives for the benefit of their babies. The successful triad of medical nutritional therapy, exercise, and insulin therapy for GDM is essential not only to achieve healthy babies but also to assure that generations to come will begin life with normal metabolism, and thus future metabolic aberrancy is reduced in the offspring.⁴⁴⁻⁴⁷

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19 Pharmacologic treatment of gestational diabetes mellitus: When to start and what agent to use

Celeste P. Durnwald and Mark B. Landon

The mainstay of gestational diabetes mellitus (GDM) management is dietary therapy, exercise, and self-monitoring of blood glucose. Nutritional management focuses on a carbohydrate-restricted diet consisting of 35%–40% of calories from carbohydrates and the remainder of calories divided between protein (20%) and fat (40%). The general recommendation for daily glucose monitoring is four times daily performed as fasting and either 1 or 2 hours after the beginning of each meal. The American Congress of Obstetricians and Gynecologists endorses glycemic targets of a fasting glucose ≤ 95 mg/dL, 1 hour postprandial ≤ 140 mg/dL, and 2 hour postprandial ≤ 120 mg/dL as measures of adequate control.¹ The American Diabetes Association endorses similar pre- and postprandial levels.² These thresholds have been extrapolated from recommendations for pregnant women with pregestational diabetes. Institution of strict glycemic control has been demonstrated to reduce neonatal morbidity and mortality associated with the diabetic pregnancy by decreasing the incidence of stillbirth and macrosomia.^{3,4} Infants born to women with well-controlled diabetes also have fewer neonatal complications such as respiratory distress syndrome, hypoglycemia, and hyperbilirubinemia.⁵ Treating GDM has also shown maternal benefit including a decrease in hypertensive disorders of pregnancy, and in one trial, a reduction in cesarean delivery was observed.⁶ Approximately, 50% of women will meet these glycemic target values within the first 2 weeks of dietary therapy, but only an additional 10% will achieve euglycemia by the fourth week.⁷ Most clinicians use this time frame to determine dietary failure and to initiate pharmacologic therapy. There is no conclusive evidence for the threshold number of blood glucoses above target or the absolute blood glucose value at which a clinician should initiate pharmacologic therapy.⁸ In our practice, if more than a third of finger-stick glucoses are above the target range, pharmacologic therapy is initiated.

Once the decision to initiate medication treatment is made, the clinician must decide which pharmacologic agent

to use. For years, the gold standard for treating women with GDM who fail to achieve euglycemia on dietary management alone has been insulin injections. Women with GDM have endogenous insulin production but are unable to either mount the twofold to threefold increase in insulin secretion or to overcome the insulin resistance of pregnancy in order to maintain euglycemia. Therefore, oral hypoglycemic agents can also be considered as options for treatment. In recent years, investigations have focused on examining the use of both glyburide and metformin.

Oral hypoglycemic agents

The rationale for oral hypoglycemic use in pregnancy is appealing to both the woman diagnosed with GDM and the clinician. Advantages of oral hypoglycemic agents include less patient discomfort, fewer supplies, and less office infrastructure needed that may lead to increased patient satisfaction and compliance with pharmacologic therapy. In addition, prescribing glyburide has been shown to be more cost-effective compared with insulin injections.⁹ The average cost savings per patient based on wholesale drug costs and hospital costs was \$165.84. When comparing new pharmacologic treatments with the previously accepted standard for management, one must consider the maternal–fetal unit in its entirety. Therefore, clinical efficacy in regard to maternal glycemic control must be addressed, as well as transplacental passage and perinatal outcomes.

Glyburide

Glyburide is a second-generation secretagogue that increases insulin secretion and sensitivity in peripheral tissues. It also reduces hepatic insulin clearance by binding to pancreatic beta cell ATP-sensitive calcium channel receptors. Therefore, it is a reasonable option for the treatment of GDM in women

who have underlying beta cell dysfunction. Glyburide typically lowers blood glucose by approximately 20% and works best in those individuals who are normal in weight to slightly overweight. It is well absorbed and not dependent on food intake with a primary side effect of hypoglycemia, although fairly low. A typical starting dose is 2.5 mg with a maximum dose of 20 mg, usually dosed once or twice daily. Although the majority of studies published using glyburide for the treatment of GDM in pregnancy utilize this once or twice daily dosing, based on the Obstetric-Fetal Pharmacology Research Units Network findings, there is new insight into timing and number of doses.¹⁰ First, glyburide concentrations begin to increase within 30–60 minutes, peak in 2–3 hours, and return to baseline by 8 hours. Based on these findings, it appears glyburide would work best if dosing regimens are adjusted to approximately 1 hour prior to the meal to allow for maximum coverage of the drug for postprandial glycemic excursion. In addition, a predinner dose may be necessary in some women. These practical points regarding administration of the medication should be discussed at the time of initiation. Glyburide is primarily metabolized by the liver. The oral clearance of the drug from plasma is at double the rate of oral clearance in nonpregnant individuals, most likely related to the metabolism of glyburide primarily from the cytochrome P450 system that is upregulated in pregnancy. Therefore, plasma drug levels in pregnancy are 50% lower compared with nonpregnant individuals.¹⁰

Maternal glycemia and perinatal outcomes

The landmark randomized clinical trial (RCT) comparing glyburide and insulin for clinical efficacy in women with GDM was conducted by Langer and colleagues.¹¹ Women diagnosed with GDM between 11 and 33 weeks who failed dietary management were randomly assigned to glyburide or insulin. In this predominantly Hispanic population, there was no difference in glycemia between groups as seen with fasting, preprandial, and postprandial values. A 4% failure rate was identified in which women were unable to achieve adequate glycemic control on maximum dosing of glyburide necessitating a switch to insulin therapy. Although the study was not adequately powered to evaluate neonatal outcomes, rates of large for gestational age (LGA), macrosomia, and neonatal

hypoglycemia were similar between groups. Glyburide was not detected in the cord serum of any infant with the mean time from the last dose of glyburide to cord blood sampling of 8 ± 4 hours. Additionally, in 12 randomly selected women in the glyburide group, glyburide was measured at the same time in maternal and cord serum. Maternal serum concentrations ranged from 50 to 150 ng/mL, whereas glyburide was undetectable in cord serum. In a secondary analysis of the parent study, the clinical efficacy of glyburide was comparable to insulin regardless of GDM severity as defined by the fasting value on 3 hour oral glucose tolerance test (OGTT).¹² The majority of women with a fasting glucose value ≤ 100 mg/dL were able to achieve glucose control with low-dose glyburide (≤ 10 mg). In contrast, for those with higher fasting values ≥ 106 mg/dL, the number of women requiring low and high dose (>10 mg/dL) were similar. There was no significant difference in the rates of LGA, macrosomia, or metabolic complications in the neonates of the treatment groups.

Since the publication of the RCT, several prospective cohort studies and retrospective reviews have evaluated the use of glyburide outside the constraints of a large RCT.^{13–17} In these studies, failure rates are closer to 20% with rates of macrosomia similar to those seen with insulin therapy (Table 19.1). These smaller studies have identified predictors of glyburide failure to include both a diagnosis of GDM earlier in pregnancy and a need for pharmacologic therapy earlier in pregnancy, higher mean fasting and 1-hour postprandial glucoses in the week prior to initiating therapy, and higher values on the 3-hour OGTT. Specifically, Conway identified that women with fasting glucose >110 on 3-hour OGTT were 50% more likely to fail glyburide therapy.¹⁴ In Kahn's study, women with GDM diagnosis <25 weeks of gestation had an eightfold risk of glyburide failure after controlling for fasting blood glucose, gravidity, and parity.¹⁶

The most common side effect of pharmacologic therapy in GDM management is maternal hypoglycemia. In the original RCT by Langer, the rate of hypoglycemia in women treated with glyburide (2%) was significantly less than their counterparts treated with insulin (20%), $p < 0.03$.¹¹ Yogeve also examined the prevalence of undiagnosed asymptomatic hypoglycemia in women with GDM treated with insulin and glyburide after at least 2 weeks of therapy.¹⁸ Using continuous

Table 19.1 Studies evaluating rates of macrosomia, failure rate of glyburide, and clinical characteristics associated with glyburide failure

	<i>n</i>	Failure rate (%)	Macrosomia (%)	Predictors of failure
Chmait et al. ¹³	69	19	17	Earlier gestational age at diagnosis Higher glucose levels
Conway et al. ¹⁴	75	16	11	Gestational age treatment initiated Higher values on OGTT
Kremer and Duff ¹⁵	73	19	19	Not evaluated
Kahn et al. ¹⁶	95	19	7	Earlier gestational age at diagnosis
Yogeve et al. ¹⁷	124	25	6.5	Higher weight gain GCT > 200 mg/dL

glucose sensing device for 72 hours, the 25 women treated with glyburide had an average of half the number of asymptomatic hypoglycemic episodes each day defined as a blood sugar less than 50 for 30 minutes compared with the 30 women treated with insulin. In women treated with insulin, 84% of hypoglycemic episodes were nocturnal compared with glyburide treated women in which the episodes were equally divided between night and day. Brustman and colleagues examined if the rate of hypoglycemia was dose dependent.¹⁹ In this study, 33% of glyburide-treated women had at least one episode of documented hypoglycemia <50 mg/dL, but no episodes of symptomatic or severe hypoglycemia. There were no significant hypoglycemic episodes in either group. Often, side effect profiles of drugs can be a rate limiting factor to patient acceptability and compliance with treatment. These findings confirm the favorable side effect profile with glyburide treatment.

In 2005, Jacobsen reported on the experience of implementing glyburide use for the treatment of GDM in a large managed care setting.²⁰ This was a retrospective review of women treated with insulin and glyburide after a diagnosis of GDM (by the National Diabetes Data Group), with exclusion for women with a fasting blood glucose >140 on 3-hour OGTT. Because of its retrospective nature, treatment groups were not matched. The insulin group ($n = 268$) was treated from 1999 to 2000 and the glyburide group ($n = 236$) was treated from 2001 to 2002. The insulin group had a 4% higher mean body mass index (BMI) and a 4% higher fasting OGTT. Glyburide was dosed starting with 2.5 mg once daily up to 10 mg, and split dosing was employed if >10 mg was required. Maternal glycemic targets were a fasting BS ≤ 100 , 1-hour postprandial ≤ 155 , and 2-hour postprandial ≤ 130 .

In evaluating maternal glycemic targets, women treated with glyburide were more likely to meet target blood sugar goals, with both lower fasting and 1-hour postprandial glucoses, which remained significant after adjustment for BMI, ethnicity, degree of glucose intolerance, and gestational age at diagnosis. Interestingly, women treated with glyburide had a higher rate of hypoglycemia and preeclampsia. The combined failure and discontinuation rate was similar to other reports ranging from 12% to 17%. Although this study was also not adequately powered to assess neonatal outcomes, there was no difference in gestational age at delivery, birth weight, fetal overgrowth (LGA and macrosomia), or neonatal hypoglycemia. Neonates in the glyburide group were less likely to be admitted to the neonatal intensive care unit (NICU), although they had a longer length of stay if admission was warranted. Neonates born to women treated with glyburide also were more likely to need phototherapy. In assessing perinatal outcomes reported, these findings suggest that glyburide can be an effective treatment in a large, diverse managed care population achieving similar results to insulin therapy.

Transplacental passage

The initial studies by Elliott using an *in vitro* cotyledon model that infused the maternal compartment with glyburide levels at higher concentrations than therapeutic human dosing demonstrated that glyburide did not cross the placenta

in significant amounts.²¹ In a follow-up study by the same group, they compared placental transfer of glyburide to first-generation sulfonylureas, showing that glyburide's high molecular weight, high plasma protein binding, and short half-life were favorable characteristics in limiting its transplacental passage.²² More recently, both Kraemer and Hebert have published conflicting results. Kraemer's placental perfusion studies documented substantial fetal-to-maternal transfer of glyburide against a concentration gradient strongly implying active transport.²³ Hebert, in work conducted through the Obstetric-Fetal Pharmacology Research Unit Network, reported that glyburide crosses the placenta with an average cord-to-maternal plasma concentration ratio of 0.7 demonstrating that umbilical cord concentrations averaged 70% of maternal concentrations.²⁴ This relationship persisted over various time intervals from the last maternal dose, although both concentrations were quite low due to the elapsed time since last dosing before delivery. The difference in results between the two groups is attributed to the different assay methodologies used, in which the high-performance liquid chromatography assay used by Hebert is a more sensitive technique than the UV detection used in the older study by Elliott. The clinical significance, if any, of placental transfer of low to moderate levels of the drug and the potential long-term effect of this fetal exposure remain unknown.

Metformin

The other hypoglycemic agent studied for the treatment of GDM is metformin, a biguanide. It inhibits hepatic gluconeogenesis, increases intestinal glucose absorption, and stimulates glucose uptake in the liver and peripheral tissues. Metformin does not stimulate insulin secretion or release and, therefore, does not cause hypoglycemia. It reaches peak concentrations in 3–4 hours and has a half-life of 2–5 hours. Ninety percent of the drug is excreted within 12 hours of administration. Typical dosing regimens include a starting dose of 500 mg once or twice daily with a slow incremental dose increase over 2 weeks to achieve desired glycemia with a maximum dose of 2500 mg. This slow increase limits the unattractive gastrointestinal side effects, such as diarrhea and flatulence in addition to its most concerning side effect of lactic acidosis, which is quite rare.

Maternal glycemia and perinatal outcomes

The RCT by Rowan evaluated metformin compared with insulin for the treatment of GDM (the MiG Trial).²⁵ In this RCT, women diagnosed with GDM after a 2-hour 75 g oral glucose tolerance test between 20 and 33 weeks were assigned to metformin versus insulin therapy. In the MiG Trial, the primary outcome of the study was a composite neonatal outcome including neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5 minutes Apgar score less than 7, or prematurity. The study was powered to detect a 33% difference between treatment groups. Secondary outcomes studied included neonatal anthropometry, maternal glycemic control, hypertensive disorders of pregnancy, postpartum glucose tolerance, and patient acceptability.

The rate of the primary composite outcome was similar in those treated with metformin compared to insulin (32% vs. 32.2%, respectively).²⁵ Only preterm birth was higher in the metformin group (12.1% vs. 7.6%, $p = 0.04$). This increase in preterm birth was related to an increased number of spontaneous preterm births, which may be due to chance or some yet to be determined effect of metformin. There was no significant difference in birth weight, rates of fetal overgrowth, or neonatal anthropometric measurements. Umbilical cord serum insulin concentrations were also similar between groups. Although this finding should be interpreted with caution as only half of the infants had cord blood levels assessed.

In regard to maternal glycemia, both fasting and 2-hour postprandial blood sugars were similar between groups. Although metformin had great patient acceptability, with 92.6% of women who were randomized to the drug continuing therapy, 46.3% of women required supplemental insulin. Women who required supplemental insulin had a higher BMI and higher blood glucoses prior to treatment. The rates of the primary outcome did not differ between those treated with metformin and supplemental insulin (34.5%) compared with women on metformin monotherapy (29.7%). Maternal weight gain from randomization to 36–37 weeks was significantly less in those randomized to metformin compared with insulin. This may play an important role in patient counseling and the advantages of using metformin for the treatment of GDM.

Since the seminal RCT by Rowan, a few smaller randomized trials have been published (Table 19.2).^{26–29} These studies are limited by small sample size and the differences in diagnostic criteria for both GDM and dietary failure, in addition to the primary outcomes studied. Both Niromanesh and Spaulonci focused on maternal glycemic control as the primary outcome, while Ijas and Tertti focused on neonatal birth weight and rates of macrosomia. In these studies, the rates of need for supplemental insulin were between 14% and 32%, which is less than 46% reported in the MiG Trial. Similar to the large RCT, women who required insulin supplementation were more likely to have a higher BMI and higher pretreatment glucose values. Other patient characteristics associated with supplemental insulin usage included higher fasting values on the diagnostic oral glucose tolerance test and an earlier gestational age at both the time of

GDM diagnosis and the time of dietary failure. Women randomized to metformin had less weight gain during the pregnancy, but this finding was not consistently reported. Rates of fetal overgrowth were similar between those treated with metformin and insulin.

Transplacental passage

Likely the biggest drawback of metformin use in pregnancy is that it freely crosses the placenta due to its low molecular weight, hydrophilic properties, and lack of protein binding. Umbilical cord concentrations of the drug have been shown to be up to twice those seen in maternal serum.³⁰ The fetal effects, whether beneficial or detrimental as an insulin sensitizer, remains largely unknown. It has been proposed that in utero exposure to metformin may enhance the action of fetal insulin and prevent adverse fetal effects or alternatively, exposure could increase the likelihood of diabetic fetopathy.

Glyburide versus metformin

Two small RCTs have compared glyburide and metformin for the treatment of GDM. In the first randomized trial, glycemic efficacies of 74 women with GDM treated with glyburide and 75 women with GDM treated with metformin were analyzed.³¹ In those women who achieved adequate control, mean fasting and 2-hour postprandial glucoses were similar between treatment groups. However, the failure rate was 2.1 times higher in those receiving metformin compared to glyburide (34.7% vs. 16.2%, $p = 0.01$, respectively). Despite this failure rate, infants born to women treated with metformin weighed significantly less than those born to women treated with glyburide (3103 ± 600 vs. 3330 ± 334 g), although the overall rate of LGA was similar between groups.

In the report by Silva and colleagues, 96 women with GDM were randomized to glyburide and 104 women with GDM to metformin.³² During treatment, maternal fasting and postprandial glucose levels were similar between oral hypoglycemic groups. In contrast, the failure rate was similar in both women treated with glyburide and metformin (29% vs. 21%). Similar to Moore's findings, infants born to women treated with metformin had significantly lower birth weights (3193 ± 521 vs. 3387 ± 512 g, $p = 0.01$, respectively), yet the rate of LGA was similar between groups. Interestingly, the ponderal index of neonates born to women

Table 19.2 Randomized controlled trials comparing metformin and insulin use in the treatment of gestational diabetes

	<i>n</i>	Supplemental insulin (%)	Macrosomia (%)*
			Metformin versus insulin
Ijas et al. ²⁶	50 metformin/50 insulin	32	19.1 versus 22
Niromanesh et al. ²⁷	80 metformin/80 insulin	14	3.8 versus 10
Spaulonci et al. ²⁸	47 metformin/47 insulin	26	0 versus 6.5
Tertti et al. ²⁹	110 metformin/107 insulin	21	4.5 versus 0.9

* All p values <0.05.

treated with metformin was significantly less compared with those born to women treated with glyburide (2.87 vs. 2.96, $p = 0.05$). Rates of neonatal hypoglycemia, defined as a blood glucose <40 mg/dL, were also similar between groups in both studies.

These two trials are limited by small sample sizes and inconsistent results. It is thus difficult to make any definitive conclusions regarding the choice of oral hypoglycemic based on the results. The greatest limiting factor to using metformin preferentially over glyburide remains the concern for the unknown effects of transplacental passage. However, it should be noted that the large RCT conducted by Rowan and colleagues was adequately powered to assess a composite neonatal outcome. This is in contrast to the RCT evaluating glyburide use in pregnancy in which the primary outcome was maternal glycemic efficacy. Further investigations would be helpful to better elucidate both short- and long-term effects of fetal exposure to oral hypoglycemic agents.

Insulin therapy

Insulin replacement is designed to mimic the normal physiologic release of insulin by the pancreas and is typically divided into basal and prandial insulin. Basal insulin is designed to restrain hepatic glucose production between meals and in the fasting state. Prandial insulin reduces glucose excursions associated with feeding. Unlike women with preexisting diabetes, insulin therapy for a woman with GDM is often tailored to address the individual glucose profile of the woman with GDM. The prescribed insulin regimen may include as few as one and as many as four insulin injections. In those women with isolated fasting glucose elevations, a single nighttime injection of basal insulin may be adequate. In women with both fasting and postprandial elevations, a multiple insulin injection regimen is necessary. In these cases, the typical starting dose would be 0.8–1.0 units/kg daily, in divided doses using both basal and prandial insulins depending on gestational age.

Over the past few years, clinical experience with insulin analogues in pregnancy has increased dramatically.

The majority of data published on insulin analogue use in pregnancy pertains to the treatment of women with preexisting diabetes, most specifically type 1 diabetes. However, the tenets of therapy and clinical experience with these newer insulin formulations can be extrapolated for the treatment of women with GDM. Certain aspects of treatment, such as congenital malformation risk, are not as pertinent to GDM because the diagnosis occurs beyond the period of organogenesis. However, transplacental passage, immunogenicity, and clinical efficacy, in addition to maternal and neonatal outcomes, will be similar regardless of diabetes type.

Prandial insulin

Prior to the introduction of insulin analogues, women with GDM were treated with the standard insulins, neutral protamine hagedorn (NPH) and regular insulin. In regard to prandial insulin, regular insulin has almost exclusively been replaced by the rapid-acting insulin analogues (RAIAs), insulin lispro and aspart. RAIAs are the preferred choice for short-acting insulin due to their superior pharmacologic profiles, which leads to greater flexibility and convenience of dosing. This has resulted in greater patient satisfaction and improved quality of life that could lead to a higher patient acceptability of insulin as a therapy.

Rapid-acting insulin analogues

RAIAs are the result of recombinant DNA technology. Unlike regular insulin, which is a hexameric molecule, RAIAs quickly dissociate into monomers in the subcutaneous tissue, which allows for a shorter onset of action, peak action, and duration of action. The duration of action of standard insulins and insulin analogues is outlined in Table 19.3. The pharmacokinetic and pharmacodynamic properties of RAIA result in twice the maximum concentration of insulin in approximately half the time compared with regular insulin (Figure 19.1), leading to less mean glucose excursion in response to a food bolus and less hypoglycemia between meals. This superior drug profile allows maximum flexibility and convenience in dosing resulting in greater patient satisfaction and improved quality of life.³³

Table 19.3 Pharmacologic profiles of standard insulins and insulin analogues

	Onset of action	Peak action	Duration of action
Standard			
Regular	30–60 minutes	2–3 hours	8–10 hours
NPH	2–4 hours	4–10 hours	12–18 hours
Rapid-acting analogues			
Lispro	5–15 minutes	30–90 minutes	4–6 hours
Aspart	5–15 minutes	30–90 minutes	4–6 hours
Glulisine	5–15 minutes	30–90 minutes	4–6 hours
Long-acting analogues			
Glargine	2–4 hours	None	20–24 hours
Detemir	3–4 hours	None	20 hours

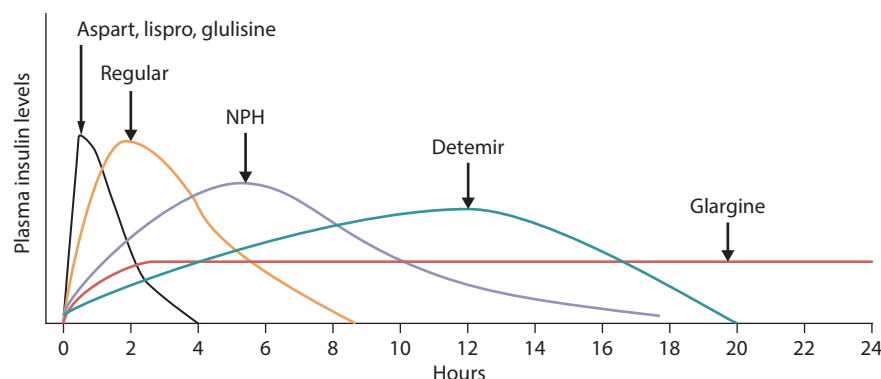


Figure 19.1 Pharmacodynamic profile of standard insulin and insulin analogues.

The RAIAs include insulin lispro, insulin aspart, and insulin glulisine. Of the rapid-acting analogues, insulin lispro is the most studied in pregnancy. A limited number of studies have also evaluated insulin aspart use in pregnancy, and no clinical studies to date have been published on insulin glulisine in pregnancy. Due to the similar pharmacologic action, the clinical experience related to transplacental passage, glycemic efficacy, and perinatal outcomes would not likely to be different based on the specific rapid-acting analogue used to treat women with GDM.

Maternal glycemia and perinatal outcomes

In the first study of women with GDM treated with insulin lispro, areas under the curve for glucose, insulin, and C-peptide were significantly lower in those women treated with insulin lispro compared to the regular insulin group, despite a similar hemoglobin A1c level.³⁴ Women with GDM treated with insulin lispro experienced fewer hypoglycemic episodes defined as blood glucose <55 mg/dL. In a retrospective review of 53 women with GDM and 33 pregestational women, mean hemoglobin A1c during pregnancy was similar in those treated with insulin lispro compared to regular insulin.³⁵ However, when the 53 women with GDM were evaluated separately, those treated with insulin lispro had lower hemoglobin A1c levels compared with those treated with regular insulin (5.25 ± 0.8 vs. 6.5 ± 2.0 , $p = 0.013$).

The majority of studies published on insulin lispro use during pregnancy have focused on women with pregestational diabetes. These analyses have demonstrated conflicting results with some studies showing no improvement in hemoglobin A1c with the use of insulin lispro^{36,37} and others showing significantly lower predelivery A1c, without an increase in hypoglycemic episodes.³³ The largest report of insulin lispro use in pregestational gravidas showed an improvement in hemoglobin A1c values throughout pregnancy. Hemoglobin A1c of women treated with insulin lispro decreased from a mean of 8.9 ± 4.2 mg/dL in the first trimester to 6.2 ± 2.4 mg/dL in the third trimester without an increase in hypoglycemia compared to those treated with regular insulin.³⁸ In a prospective observational study of 58 pregestational women treated with insulin lispro and 49 with regular insulin of similar age, BMI, and vascular complications, total insulin requirements in each trimester were

lower in women treated with insulin lispro.³⁹ Yet the rate of increase in insulin between trimesters was similar between groups. Predelivery hemoglobin A1c was improved in those treated with insulin lispro compared with regular insulin (5.9 ± 1.0 vs. 6.7 ± 1.3 mg/dL, $p = 0.02$). In contrast, a recent retrospective, multicenter Italian study reported a significant improvement in hemoglobin A1c levels in the first-trimester women treated with insulin lispro compared with regular insulin ($6.7\% \pm 1.3\%$ vs. $7.3\% \pm 1.4\%$, $p < 0.001$), but similar A1c levels in both treatment groups in the third trimester.⁴⁰ Rates of severe hypoglycemic episodes were similar.

Two recent studies have evaluated maternal obstetrical outcomes for women with preexisting diabetes undergoing lispro treatment in pregnancy. Both studies have shown similar rates of preeclampsia, preterm birth, and cesarean delivery in those treated with insulin lispro compared with regular insulin.^{39,40} In regard to neonatal outcomes, rates of shoulder dystocia, NICU admission, respiratory distress syndrome, and neonatal hypoglycemia were comparable.⁴⁰ Insulin lispro has a great homology with insulin growth factor 1 (IGF-1) raising concern for the possibility of accelerated fetal growth with in utero exposure to this RAI. Table 19.4 shows the rates of fetal overgrowth and mean maternal glycemia as measured by hemoglobin A1c in pregnancies treated with insulin lispro, the majority of which are in women with pregestational diabetes. Similar rates of macrosomia have been reported in pregnancies treated with insulin lispro and regular insulin.^{35,36,39–42} From the culmination of these reports, insulin lispro does not appear to be associated with higher rates of fetal overgrowth than would be expected in diabetic pregnancy.

To date, only one study has evaluated anthropometric characteristics of newborns exposed to insulin lispro in utero.⁴³ This study enrolled 49 pregnant women with GDM, randomly assigned to treatment with insulin lispro or regular insulin, and 50 pregnant women with a normal glucose challenge test, matched for age, parity, prepregnancy weight, and BMI. Rates of LGA and small for gestational age (SGA) infants were similar between groups. However, the rate of infants with a cranial–thoracic circumference ratio between the 10th and 25th percentile was significantly less in women treated with insulin lispro compared with regular insulin (12% vs. 37.5%). This rate was comparable to the rate seen

Table 19.4 Maternal glycemia and rates of fetal overgrowth with insulin lispro use in pregnancy

Author	Year	n	Mean A1c ^a (mg/dL)	Rate of LGA (%)
Aydin et al. ³⁵	2008	27 lispro	6.3 ± 2.2	7.4
		59 regular	7.1 ± 2.1	13.6
Lapolla et al. ⁴⁰	2008	72 lispro	7.4 ± 1.7	55.1
		298 regular	7.4 ± 1.5	39.2
Durnwald and Landon ³⁹	2008	58 lispro	7.1 ± 2.2	32.8
		49 regular	8.3 ± 2.6	20.4
Cypryk et al. ³⁶	2004	25 lispro	7.8 ± 1.4	43.5
		46 regular	7.5 ± 1.5	30.3
Masson et al. ⁴²	2003	71 lispro	7.4 ± 1.7	35
Garg et al. ⁴¹	2003	61 lispro	7.2 ± 0.2	24
Persson et al. ³⁷	2002	16 lispro	6.5	No difference
		17 regular	6.6	

^a First trimester or overall, if first trimester not reported.

in those with normal glucose tolerance (14%). In this study, 1-hour postprandial glucoses in the lispro group were close to the physiologic levels as demonstrated by women with normal glucose tolerance. In the regular insulin group, 1-hour postprandial glucoses were higher than both women with normal glucose tolerance and women with lispro-treated GDM. The level of glycemia may have contributed to the aberration in fetal growth pattern seen in this group. Although interesting, further investigation is needed on a larger scale before any conclusions can be made whether the difference in anthropometry is an effect of treatment with insulin lispro.

Pettitt and colleagues were the first to study the clinical efficacy of insulin aspart compared to regular insulin in 15 women with GDM.⁴⁴ In this study, peak insulin and glucose concentrations were measured after eating a breakfast meal for three consecutive days: the first when no insulin was given, the second with a random assignment to either regular insulin or insulin aspart, and the third when the other insulin preparation was administered. Peak insulin concentrations were higher, and peak glucose concentrations were lower with both insulins compared with no insulin. Glycemic control, as measured by the glucose concentration under the curve above baseline, was significantly improved for insulin aspart compared with no insulin. In a follow-up study of 27 women with GDM randomized to treatment with insulin aspart versus regular insulin, there was a greater reduction in average glucose values from baseline in those treated with aspart indicative of improved postprandial glycemic control.⁴⁵ There were more hypoglycemic episodes (71%) associated with aspart use, although no severe hypoglycemic event were noted. Treatment with insulin aspart was also associated with significantly lower levels of C-peptide compared with regular insulin, reflecting a lower demand on beta cell function. This is likely attributed to the higher peak insulin concentrations that were achieved in this treatment group. Insulin-specific antibody binding was low in both groups (<1.5%).

The largest evaluation of insulin aspart use in pregnancy was an open-label, randomized, parallel group study of 322 women with type 1 diabetes conducted at 63 sites in 18 countries.⁴⁶ Study entry required a hemoglobin A1c of ≤8% at pregnancy confirmation. In this study, the mean of the difference between preprandial and postprandial plasma glucoses were lower for those women receiving insulin aspart, despite comparable hemoglobin A1c levels. Despite similar mean total amount of insulin in both groups, mean daily requirement of prandial insulin was significantly lower in the insulin aspart group. There was no difference in hypoglycemic episodes between groups. Maternal outcomes such as rates of preeclampsia, preterm labor, and cesarean section were similar between groups. In contrast, women treated with insulin aspart reported significantly greater satisfaction with their assigned treatment as measured by the Diabetes Treatment Satisfaction Questionnaire. In a second report, 137 infants born to women treated with insulin aspart and 131 infants born to women treated with regular insulin were evaluated. Rates of fetal overgrowth, neonatal hypoglycemia, and perinatal mortality were similar between groups.⁴⁷

Transplacental passage

Transplacental passage of insulin can occur when insulin complexes with immunoglobulins to form an antigen-antibody complex. Previous studies have linked transplacental passage of insulin complexes with fetal overgrowth. Jovanovic first reported on the immunologic effects and placental transfer of insulin lispro in women with GDM.³⁴ In this study, anti-insulin antibody levels were similar in both groups, both at enrollment and delivery. Insulin lispro was undetectable in the umbilical cord blood, including four women who received continuous intravenous administration of the drug during labor. There were no cases of fetal anomaly, macrosomia, or neonatal hypoglycemia. Similarly, in a subset of 95 women enrolled in a randomized trial of aspart and regular insulin, analysis of maternal and cord

blood insulin antibody levels demonstrated low levels of insulin-specific antibodies in both insulin groups at baseline and delivery.⁴⁸ In this analysis, insulin aspart was undetectable in all cord blood samples evaluated.

Two in vitro perfusion studies have evaluated the transfer of insulin lispro across the human placenta.^{49,50} In the first study, the placental transfer of a range of insulin lispro concentrations was examined. The maternal side of the placenta was perfused with constant concentrations of the drug and the fetal circulation was closed. No placental transfer of lispro was detected during perfusion with 100–200 μ U/mL. Although there was a possibility of transfer with concentrations mimicking a single subcutaneous dose of over 50 units that was maintained for greater than 60 minutes, there was no placental transfer at single standard doses.⁴⁹ Given the half-life of insulin lispro, it is unlikely that this physiologic state could be reproduced in the clinical setting, and therefore, insulin lispro does not appear to cross the placenta in any significant amount. The lack of transplacental passage was also confirmed on a smaller scale by Holcberg.⁵⁰ No in vitro perfusion studies have evaluated the transfer of insulin aspart across the human placenta. Given the similar biochemical characteristics, it is likely that the findings reported with insulin lispro would be similar to those of insulin aspart if such studies were conducted.

Basal insulin

In the majority of women with GDM, the basal insulin primarily prescribed continues to be the intermediate acting insulin, NPH insulin. In most women, the greater insulin resistance associated with GDM and subsequent higher insulin requirements cannot be adequately treated with a single dose of a long-acting insulin analogue (LAIA) such as glargine or detemir, which are peakless. If LAIAs are used, it is not uncommon for women with GDM to require twice daily dosing. There is limited experience in pregnancy with LAIA. Similar to the RAIA, the reports published focus on the treatment of women with preexisting diabetes, most specifically type 1.

Long-acting insulin analogues

The biochemical properties of the LAIA allows for a slow, constant release of insulin without a pronounced peak in insulin concentrations. The relatively flat activity profile is beneficial for women at significant risk for nocturnal hypoglycemia. One of the biggest advantages of the LAIA is less hypoglycemia. The once-daily dosing regimens also may enhance patient acceptance and satisfaction. In studies of nonpregnant diabetics, insulin detemir has been shown to have more consistent insulin absorption compared with both insulin glargine and NPH insulin.⁵¹ Compared with insulin glargine, detemir is similarly peakless but exhibits a slightly shorter duration of action and therefore is dosed every 12 hours in most diabetics.

Maternal glycemia and perinatal outcomes

Studies evaluating the use of glargine in pregnancy have primarily been limited to retrospective reviews and observational cohorts of women with type 1 diabetes.

Four studies have evaluated women diagnosed with GDM treated with insulin glargine.^{52–55} All studies included a mixed population of women with pregestational diabetes and GDM. In a prospective cohort study of 82 women with GDM randomly assigned to either insulin glargine or NPH, the total dose of basal insulin was less in those women treated with glargine. Fasting glucose levels in the 36th week of gestation were also lower in the glargine group. Rates of maternal hypoglycemia and hypertensive disorders of pregnancy were higher in those women treated with NPH. In regard to neonatal outcomes, jaundice was more common in the NPH-treated group, but no differences were noted in the rate of macrosomia or LGA, neonatal hypoglycemia, respiratory distress syndrome, or 5-minute Apgar <7.⁵² In a smaller retrospective review of a mixed population of 112 women with pregestational diabetes and GDM treated with glargine compared with NPH, there was no significant difference in maternal complications of preeclampsia, hypoglycemia, or cesarean delivery between treatment groups in the 59 women with GDM studied.⁵³ Rate of LGA infants, Apgar scores, neonatal hypoglycemia, and hyperbilirubinemia, as well as NICU admission, were also similar between groups. However, only 15 of the 59 women with GDM were treated with glargine.⁵³ In two additional retrospective reviews including a small number of women with GDM, perinatal outcomes were similar in women treated with NPH insulin and insulin glargine.^{54,56}

Clinical experience with insulin detemir in pregnancy is limited to case reports and one RCT of women with type 1 diabetes.^{57–59} In this RCT, the efficacy of insulin detemir compared with NPH insulin (both with prandial insulin aspart) was evaluated. Of 310 women with type 1 diabetes, 152 were randomly assigned to insulin detemir and 158 to NPH up to 1 year prior to pregnancy or during the 8th–12th week of pregnancy. Maternal hemoglobin A1c at the 36th week was similar between groups. However, fasting plasma glucoses were lower in women treated with insulin detemir at both 24 weeks and 36 weeks of gestation. There was no difference in maternal hypoglycemic episodes. In a follow-up study of the neonates born to the women in the RCT, neonatal outcomes including congenital malformations, fetal growth disturbance (SGA and LGA), preterm delivery, and neonatal hypoglycemia were similar between treatment groups.⁶⁰

There has been concern raised about the increased affinity to IGF-1 that is demonstrated by insulin glargine compared to human insulin with a potential to stimulate fetal growth. A retrospective review in which 77% of the study population was diagnosed with GDM evaluated the use of insulin glargine on select neonatal outcomes.⁵⁵ This analysis reported a mean birth weight of 3142 ± 606 g for the study population, with a 2% incidence of macrosomia in GDM women. In addition, none of the studies published to date demonstrate an increase in the rate of LGA infants or fetal macrosomia with glargine treatment. In contrast to glargine, insulin detemir has a low affinity for the IGF-1 receptor (approximately 1/10 that of human insulin). Although a strictly GDM population has not been studied, the risks of fetal overgrowth and macrosomia are not unique to abnormal glucose metabolism of the GDM cohort.

Transplacental passage

Results from human placental cotyledon models of uncomplicated term pregnancies have shown that there is no transplacental passage at maternal therapeutic concentrations of insulin glargine.⁶¹ Transport across the placenta was demonstrated at concentrations 1000-fold higher than clinically therapeutic levels, yet there was a significant difference in the rate of disappearance from the maternal compartment compared with the rate of appearance in the fetal compartment. This suggests that the placenta may sequester some amount of insulin glargine at concentrations at these high levels.

Published studies evaluating glargine use in pregnancy are limited by small sample size, a mixed population of GDM, and pregestational women studied and do not show a consistent clinical benefit for the use of insulin glargine in the pregnant women. Given these findings, there is little justification to choose glargine over NPH for basal insulin for the treatment of GDM. Although there is also limited

published data on the use of insulin detemir in GDM as well, the results are more convincing given the RCT of women with preexisting diabetes.

Conclusion

Pharmacologic treatment of GDM should be designed to achieve euglycemia that has been linked to both maternal and neonatal benefit. Diagnosis of dietary failure should be prompt and initiation of pharmacologic therapy expedited in those women unable to achieve glycemic targets on nutrition therapy alone. Both insulin therapy and oral hypoglycemic agents are viable options. Treatment strategies should be individualized based on a woman's glycemic profile, clinical characteristics, and fetal growth projection. Ideally, therapies should be aimed at lowering the demand on beta cell function during this time of physiologic stress.

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20 Gestational diabetes mellitus: The consequences of not treating

Oded Langer

GDM dilemma

It is self-evident that women with type 1 and type 2 poorly controlled diabetes have a significant increase in adverse perinatal outcome in comparison to nondiabetic patients. The condition is especially detrimental when the targeted level of glycemia is not achieved. It is also realistic to assume that similar adverse outcomes will result in gestational diabetes mellitus (GDM) since it is a looking-glass image of type 2 diabetes. Since the late 1960s when O'Sullivan first suggested the term "gestational diabetes," an argumentative environment has persistently surrounded this clinical entity and its association to adverse pregnancy outcome, i.e., macrosomia, birth trauma, and metabolic complications. However, opinions and anecdotes have surpassed research-generated data.

To date, there is no consensus regarding diagnostic criteria and the utility of universal screening for GDM. Lack of accord on these issues have led to inconsistencies in results of published studies.^{1,2} For example, Jarrett concluded that GDM is "a nonentity" whose only clinical association is with an increased maternal risk of subsequent diabetes.³ Several studies and noted forums have stated that there is as yet no consensus on the definition, management, or treatment of GDM.⁴ Hunter and Milner stated "gestational diabetes is a diagnosis still looking for a disease." According to these physicians, GDM is not convincingly associated with increased perinatal mortality or morbidity, and macrosomia per se, regardless of definition, is not a morbid condition.⁵

In contrast, Beard and colleagues⁶ concluded that GDM is a clinical entity associated with a significant incidence in diabetes in the later life of the mother and an increase in fetal and neonatal morbidity. In recent years, several studies demonstrated the association of GDM with perinatal morbidity and mortality. The results of these studies demonstrated that GDM is not only a clinical entity but a disease with short- and long-term complications.⁷⁻⁹

In the current era of evidence-based medicine, it is surprising that the opposing positions are not the result of authors' researched data but based upon opinions lacking evidence to support these positions. In order to determine the research-driven answer to this dilemma, the most appropriate means would be to conduct randomized clinical trials (RCTs). However, in some cases, the RCT study design faces an ethical dilemma so an alternative design is mandated.

GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. Therefore, some of the women already have impaired glucose tolerance (IGT) test and/or impaired fasting glucose. The definition applies regardless of treatment modality and/or the persistence of the condition after pregnancy. While it is likely that maternal carbohydrate intolerance reflects a continuum of risk for adverse outcomes,^{10,11} it is not known whether there is a benefit to identification and subsequent treatment of mild levels of severe carbohydrate intolerance during pregnancy.

Since GDM is considered the major medical complication in pregnancy, empirical attempts were made to address the controversy. However, the results of many studies are derived from administrative databases, i.e., billing systems. The data should not be used for clinical studies since they may lead to erroneous conclusions.¹²

The conclusions from other studies are the result of observational design. Most reported associations in observational research are false, and the minority of associations that are true are often exaggerated. This issue is problematic for weak associations, often defined as relative risks (RRs) or odds ratios (ORs). These relationships can usually be ascribed to bias rather than to an underlying association. A prudent rule to follow in statistical analysis is to assume that unless RRs in cohort studies exceed 2-3 or ORs in case-control studies exceed 3 or 4, associations in observational study findings should not be considered credible.¹³

Change from physiology to pathophysiology

The first condition in order to establish a medical entity as a disease is to demonstrate change from normal to pathophysiology. This will facilitate the development of interventions aimed at prevention as well as treatment. Human pregnancy is characterized as an insulin-resistant condition. Although there is a fourfold to fivefold range of insulin resistance in the general population, there is a relatively uniform 40%–50% increase (from the pregravid condition) in insulin resistance and increase in insulin secretion. A substantial number of studies have addressed this topic.^{14–19}

Another factor which may contribute to increased insulin resistance during pregnancy is the rise in body fat or change in body fat distribution that begins in early gestation. It is well established that obesity per se causes insulin resistance.²⁰ It has been shown that total oxidative and nonoxidative glucose metabolism is inversely related to increased visceral-to-subcutaneous-fat ratio in obese women and to total fat content in lean women.²¹ Others have demonstrated decreased insulin sensitivity in subjects with a central pattern of fat distribution. Whatever the cause for increased insulin resistance during pregnancy in women who maintain normal glucose tolerance, it is offset by a 3- to 3.5-fold increase in insulin secretion.²² Therefore, the degree of insulin resistance during late gestation appears to be dependent primarily on pregravid maternal insulin resistance, which is quite variable, and secondarily on the 40%–50% increases mediated through placental factors.

In 1981, Bergman et al.²³ proposed that there is a predictable relationship in the shape of a rectangular hyperbola between the quantity of insulin produced by β -cells and the sensitivity of tissues to the glucose-lowering effects of insulin. Kahn et al.²⁴ demonstrated that this relationship is present across a wide range of insulin sensitivity in people with normal glucose tolerance. A hyperbolic relationship exists between insulin sensitivity and several measures of β -cell insulin release in women with IGT.²⁵ The amount of insulin released at a given level of insulin resistance is lower in people with abnormal compared with normal glucose tolerance.^{26,27} Although GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy,²⁸ the definition applies whether the condition persists after pregnancy but does not preclude the possibility that the glucose intolerance may have predated the pregnancy. Women who develop GDM are, in fact, genetically predisposed to develop type 2 diabetes since they tend to have a strong family history of the disease. Some stressors associated with pregnancy probably trigger them to develop overt disease sooner than if they had not become pregnant.

Similar to other groups genetically susceptible to type 2 diabetes, women with previous GDM and normal glucose tolerance have been shown to have defects in glucose metabolism. Using the hyperinsulinemic–euglycemic clamp technique, Catalano et al.^{29,30} demonstrated insulin resistance in

50% of subjects with normal glucose tolerance and previous GDM. This was primarily due to decreased nonoxidative glucose disposal. Ward et al.,³¹ using the Bergman intravenous glucose minimal model technique, also found evidence of increased insulin resistance in women with previous GDM. Unfortunately, neither Catalano nor Ward controlled for family history in the subjects, so it is unclear whether family history or previous GDM was the marker for these early abnormalities in glucose metabolism.

In summary, GDM is characterized by pathogenesis deviating from the normal physiology of pregnancy that involves insulin resistance and decreased insulin secretion. Furthermore, similarity exists between the pathogenesis of GDM and type 2 diabetes, which are probably one disease at different stages on the spectrum of glucose intolerance.

Is there an associated increased adverse outcome in GDM?

Socrates once said that the beginning of wisdom is the definition of terms. However, using different definitions for GDM diagnosis criteria or threshold for neonatal hypoglycemia will result in varying rates of the problem. Not only different definitions but also diverse institutional policies such as indication for neonatal intensive care unit (NICU) admission and for cesarean delivery will result in varying rates reported in different studies.

Small sample sizes have resulted in the evolution of the concept of composite outcomes (Tables 20.1 through 20.3). Composite outcomes are pooled individual outcomes (serious morbidities) in order to produce a single outcome (overall serious morbidity). As treatments and population health improve, the number of individual adverse outcomes has declined. Using composite outcomes can often overcome this reality by combining several outcomes, thereby increasing the efficiency of a clinical trial (power and size). Outcome selection has clinical significance; however, when evaluating composite outcomes in various studies, it is

Table 20.1 Sample sizes for various effects in the primary outcome (composite)

Outcome rate in untreated group (%)	30% reduction		40% reduction	
	Outcome rate in treated group (%)	Sample size	Outcome rate in treated group (%)	Sample size
20	14.0	611	12.0	325
25	17.5	537	15.0	248
30	21.0	366	18.0	196
35	24.5	295	21.0	159
40	28.0	243	24.0	132
45	31.5	218	27.0	110
50	35.0	169	30.0	93

Table 20.2 Prevalence of hyperbilirubinemia

Definition	Authors	Population	n	Outcome rate (%)
≥10 mg/dL	Gabbe et al.	GDM treated	261	15.7
>12 mg/dL	Hod et al.	GDM treated	731	5.2
>12 mg/dL	Magee et al.	GDM	96	15.6
		Normal	521	10.6
≥12 mg/dL	Langer et al.	GDM intense tx	1145	7.6
		GDM usual tx	1316	7.9
Not defined	Garner et al.	GDM treated	149	5.4
		GDM untreated	150	6.6
Requiring treatment	Persson et al.	Mild GDM treated	233	4.5
>12 mg/dL	Langer et al.	GDM untreated	555	11.0
		GDM treated	1110	9.0
		No GDM	1110	4.0
>95th percentile	Landon	GDM untreated	473	12.9
Not available (n.a.)	Crowter	GDM untreated	524	n.a.

Table 20.3 Prevalence of neonatal hypoglycemia

Definition	Authors	Population	n	Outcome rate (%)
<30 mg/dL if <2500 g	Gabbe et al.	GDM treated	261	6.5
<20 mg/dL if 2500 g				
<30 mg/dL up to 72 hours;	Hod et al.	GDM treated	731	5.2
<40 mg/dL later				
≤30 mg/dL × 2 <4 hours after birth	Langer et al.	GDM intense tx	1145	3.8
		GDM conventional	1316	20.0
<31 mg/dL <2 hours after birth	Jang et al.	GDM treated	65	7.7
Symptomatic	Persson et al.	Mild GDM treated	233	0.9
		GDM treated	222	2.3
<30 mg/dL <1 hour after birth	Schader-Graf et al.	GDM treated	154	40.3
40 mg/dL × 2 <4 hours after birth	Langer et al.	GDM treated with glyburide	201	9.0
		GDM treated with insulin	203	5.9
<40 mg/dL	Langer et al.	GDM untreated	555	7.0
		GDM treated	1110	14.0
		No GDM	1110	2.0
Hypoglycemia requiring I.V. therapy	Crowther et al.	GDM untreated	506	5.0
<35 mg/dL	Landon et al.	Mild GDM untreated	473	15.0

prudent to verify that the variables included in each composite outcome are identical.

In the compilation of an outcome variable, only those that are a result of GDM pathophysiology should be included; variables that reflect physician behavior, i.e., cesarean section (c/s) delivery, misrepresent the conclusion. Although associated with maternal morbidity (e.g., infection, bleeding), c/s is a physician-driven decision rather than a complication of the disease. Rates of c/s have skyrocketed with more repeat c/s's,³² c/s by demand, and elective c/s for breech delivery. Although this procedure has outstripped historical numbers for both diabetic and nondiabetic patients, c/s rates

should not be used as an outcome measure in GDM because the procedure is not directly related to disease morbidity.

Delivery through c/s has become a self-fulfilling prophecy in the treatment of GDM. Naylor et al.³³ reported that the c/s rate was 34% in women with GDM compared with 20% in women without GDM. The National Institute of Child Health and Human Development (NICHD) study⁹ resulted in 27% c/s rate in the treated versus 32% in the untreated group, while the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS)⁸ c/s data revealed 31% in the treated and 32% in the untreated group. What these numbers indicate is that inherent in the study of a treatable entity is that this

new knowledge may alter the clinician's behavior.³³ On the other hand, there are care providers who have not inevitably been influenced by the GDM diagnosis and have instead evaluated the presenting conditions of the disease.^{34,35} In our study,⁷ the c/s rate was similar for the untreated (24%) and the treated (23%) compared to 14% in nondiabetic subjects.

Neonatal complications

The adverse outcomes most commonly associated with GDM include increased perinatal mortality, macrosomia, shoulder dystocia, birth trauma, preeclampsia, c/s, neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, and polycythemia. In addition, there are long-term effects associated with GDM pregnancies such as an increased maternal risk of developing diabetes in the future and an increased risk of obesity and glucose intolerance in the offspring.

Perinatal mortality is the most significant outcome, and early, albeit flawed studies showed a fourfold increase in perinatal mortality in women with GDM. These studies failed to control for variables affecting perinatal mortality such as fetal malformations, maternal history of stillbirth, and advanced maternal age. Furthermore, these studies more than likely included women with unrecognized pregestational diabetes, thus contaminating the results. In addition, in most studies a labeling bias exists since a GDM diagnosis tends to enhance surveillance and interventions that may have a major impact on perinatal mortality. Some researchers have suggested that GDM has no or negligible effect on mortality. This could be explained by two opposing views: GDM has no or negligible effect on mortality, or due to the overall decrease in perinatal mortality, excess fetal deaths due to unrecognized GDM could go unnoticed in smaller studies.

O'Sullivan and Mahan first reported an association between GDM and perinatal death, documenting a 6.4% risk only in women with GDM who were older than 25 years of age, and a RR of 4.3 over controls.³⁶ Abell et al.³⁷ reported similar results in women with GDM with a 3.9% overall perinatal mortality rate. However, an analysis of 1016 GDM pregnancies from the same institution documented an increased perinatal mortality rate (3.2%) only among those meeting the stringent World Health Organization (WHO) criteria for the diagnosis of GDM.³⁸ Schmidt et al.³⁹ evaluated the relation between the American Diabetes Association (ADA) and the WHO diagnostic criteria for GDM against pregnancy outcome. Of the 4977 women in the study, 2.6% had GDM by the ADA criteria and 7.2% by the WHO criteria. The perinatal death in the ADA group had an OR of 3.10, 95% C.I., 1.42–6.47. Similarly, the perinatal mortality by the WHO criteria had an OR of 1.59, 95% C.I., 0.86–2.90 (nonsignificant).

Mondestin et al.⁴⁰ reported the results of a retrospective cohort study of U.S. data (1995–1997). These included 10 million nondiabetic gravidas and 271,691 diabetic patients with fetal death rates of 4/1000 and 5.9/1000, respectively. Fetal death rates increased when birth weight was >4250 g for nondiabetic and 4000 g for diabetic patients with a two-fold increased rate in mortality in the diabetic group. The

drawbacks of this study included the retrospective design and the lack of distinction between types of diabetes since the results were derived from an administrative database. However, it would be reasonable to assume that the majority of the diabetic patients had GDM that accounts for 90% of all diabetic pregnancies.

Clinicians must, therefore, consider the merits of establishing a GDM diagnosis. GDM, if untreated or not recognized, may be associated with an increased risk of intrauterine fetal death and commonly reported morbidities such as macrosomia, birth trauma, neonatal hypoglycemia, hyperbilirubinemia, hypoglycemia, and polycythemia. There is paucity of prospective data concerning some of these risks. However, it is generally agreed that women with GDM with significantly elevated fasting blood glucose levels appear to have an increased risk of intrauterine fetal death.

Macrosomia, shoulder dystocia, and birth trauma

Being relatively common and easily documented, macrosomia is the adverse perinatal outcome most investigators refer to when addressing GDM. Macrosomia is the primary outcome with relevant surrogate complications such as c/s, shoulder dystocia, and brachial plexus injury. The overall rate of macrosomia for the nondiabetic population is 7%–9%.^{28,41,42} In contrast, the incidence reported for macrosomia in GDM is management dependent. When good glycemic control is not achieved, the incidence of macrosomia can be as high as 20%–45%.³⁵ The macrosomic fetus is a result of diabetic fetopathy and is characterized by organomegaly.^{43,44} Complications, directly and indirectly associated to fetal macrosomia are neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, and polycythemia; in addition to birth trauma, these are all the consequence of not treating or inadequate treatment of the disease.

Excessive fetal growth occurs in as many as 50% of pregnancies complicated by GDM.⁴⁵ It was shown that the accelerated fetal growth is associated with the maternal glycemic profile.^{46,47} Although fetal growth can be measured by birth weight, a more accurate way to characterize overgrowth is by estimation of body composition that includes lean body mass (LBM) and fat-free mass (FFM). LBM is a metabolically active tissue and is relatively stable in utero. FFM is more variable and sensitive to factors that affect fetal growth. Therefore, to more accurately characterize the diabetic fetopathy, measurements that can identify even minimal deviations from the norm are needed. FFM and LBM may provide the means. Recent studies have shown conflicting results in the evaluation of infant body composition.^{43,48,49} Catalano reported increased FFM in infants of women with GDM even when average weight for gestational age were comparable to infants of women with normal glucose tolerance.⁴⁸ Similarly, he demonstrated increased body fat in infants of women with GDM requiring a cesarean delivery compared with normal glucose tolerance despite similar birth weights. In contrast, we and Naeye^{43,44} found an increase in LBM at

the time of autopsy in overgrown infants of women with diabetes. In a study evaluating body composition of macrosomic infants of diabetic women, we demonstrated increased body fat and decreased LBM in infants of women with GDM when compared to women with normal glucose tolerance.⁵⁰

Long-term effects of GDM. When addressing the issue of the long-term effects of GDM, one must differentiate between the long-term maternal effects and the prognosis for the offspring.

The mother

The increased risk of developing type 2 diabetes later in life in women with GDM is well known with the magnitude of the risk ranging from 20% to 50%; it is lower in Caucasians and higher in Hispanic women, those of Mediterranean or East Asian descent and the Canadian Aboriginal population. There is no evidence that the treatment of GDM will reduce this risk although recent data⁵¹ suggest that the rate of progression to type 2 diabetes can be modified by lifestyle changes, thus underscoring a possible benefit for increased surveillance of this high-risk population.

The neonate

Since Barker's primary epidemiologic studies in 1989,^{52,53} there is increasingly strong data to support the concept that many fetal stresses may lead to fetal programming and the alteration of the normal developmental gene expression pattern. Research indicates that the child of the diabetic mother remains at increased risk for a variety of developmental disturbances: obesity,^{54–56} IGT or diabetes,⁵⁷ and diminished neurobehavioral capacities.^{58–64} Therefore, it would be reasonable to speculate that the process whereby a stimulus or insult (glucose toxicity and other metabolic fuels) acting at a critical period of development in early and during intrauterine life alters gene expression patterns for life.^{65,66}

Cognitive development in children of diabetic mothers

There is paucity of data related to the cognitive development of infants of diabetic mothers. A study of infants born to 73 women with preexisting diabetes and 112 women with GDM sought to determine the relationship between maternal fasting plasma glucose and hemoglobin A1C during the second and third trimesters on neonatal performance on the Brazelton Neonatal Behavioral Assessment Scale.⁵⁸ They found a significant correlation between poor glycemic control in three out of the four newborn behavioral dimensions on the scale for both gestational and pregestational diabetics. In another study,^{67,68} they evaluated the offspring of 95 women with preexisting diabetes and 101 subjects with GDM using the Bayley Scales of Infant Development at 2 years of age and the Bruininks–Oseretsky Test of

Motor Proficiency at ages 6, 8, and 9 years. They reported that the children's average scores on the Bruininks–Oseretsky test at ages 6–9 years correlated significantly with B-hydroxybutyrate in maternal second and third trimesters. There was also a borderline association between children's scores on the psychomotor development index at age 2 and B-hydroxybutyrate. Rizzo et al.⁵⁹ correlated measures of maternal glucose and lipid metabolism (fasting plasma glucose levels, hemoglobin A1C levels, episodes of hypoglycemia and acetonuria, and plasma β -hydroxybutyrate and free fatty acid levels) with two measures of intellectual development in the offspring using the Bayley Scales of Infant Development for 2-year olds and the Stanford–Binet Intelligence Scale for 3- to 5-year olds expressed as an average of the three scores. The children's mental development index scores at the age of two correlated inversely with the mother's third-trimester plasma β -hydroxybutyrate levels; the average Stanford–Binet Intelligence Scale scores correlated inversely with third-trimester plasma β -hydroxybutyrate and free fatty acid levels.

Maternal diabetes during pregnancy may affect behavioral and intellectual development in the offspring. Petersen et al. suggested that first trimester intrauterine growth delay is associated with psychomotor deficit in the offspring at age 4–5 probably as a result of poor glycemic control.^{60,69} Sells et al. reported that late entry into treatment programs in pregnancy in preexisting diabetic women resulted in lower scores on language measures and intellectual development through age 2 in comparison to women who maintained good glucose control during pregnancy.⁶³ Stenninger et al. reported that children born to mothers with diabetes (probably GDM) who subsequently developed neonatal hypoglycemia experienced long-term neurological dysfunction. Offspring had more difficulties in validated screening tests for minimal brain dysfunction and were hyperactive, impulsive, and easily distracted. In addition, they had a lower developmental score in comparison to the offspring of normoglycemic diabetic women and nondiabetic control patients.⁷⁰ Olsson et al. concluded that impaired cognitive function may precede clinical onset of type 2 diabetes.⁷¹ In summary, the existing evidence indicates that poorer glycemic control or other shared risk factors may influence both cognitive development and the risk for type 2 diabetes. The data suggest that early detection of subclinical disease and treatment may be of value in protecting against cognitive deficits and adverse neurological outcomes in addition to the possibility of early development of metabolic syndrome (hypertension, obesity, and diabetes) when GDM is not treated or poorly managed.

Clinical studies

Care providers and their institutions repeatedly find themselves compared to one another as well as to national/universal standards. Inherent in these comparisons is that providers with improved outcomes presumably provide higher-quality care. Nonetheless, there are three major sources of distinction in outcomes: preexisting patient

characteristics, quality of care, and random variation. These factors, in addition to others, will enable the classification of GDM as a clinical entity.

There has historically been two phases in which this issue has been addressed. In the past, there has been relatively scant data; shortcomings in the few existing studies included small sample sizes and, therefore, insufficient power (increased likelihood for types 1 and 2 errors), as well as lack of controls for the confounding effects of ethnicity, maternal obesity, age, and parity. In evaluating the results of a study, it is prudent to consider the sample size and the power designated for the study. Power is the ability to detect a difference when one really exists; power increases as the sample size increases. It also precludes a type 2 error (false-negative); power of 80% is usually acceptable. However, a very small difference can achieve statistical significance if the sample size is large enough. On the other hand, a large effect may not attain statistical significance if there is substantial variability arising from a small sample size. Statistical significance does not always equate with clinical significance. These unresolved issues fanned the controversy over GDM as a clinical entity.

Roberts et al.⁷² evaluated outcomes of women with untreated IGT (7.8 mmol/L or 140 mg/dL) during pregnancy; there was an increased incidence of c/s with no differences in neonatal outcome compared with women with normal oral glucose tolerance test (OGTT). Ostlund et al.⁷³ prospectively studied women with IGT (defined as fasting blood glucose level of <6.7 mmol/L [121 mg/dL] and 2-hour blood glucose level >9 and <11 mmol/L [162–198 mg/dL]) who were undiagnosed and untreated. The obstetrician was not informed of the deviation in the glucose tolerance. They compared the untreated IGT to both the controls and treated GDMs. The rate of macrosomia (>4000 g) was 33%, 16%, and 30% and large for gestational age (LGA) 25%, 4%, and 25%, respectively. The main problem in the Ostlund study is that the authors used a nontraditional definition for GDM, which was a modification of the Lind definition.⁷⁴ Adams et al.⁷⁵ identified 16 cases of clinically unrecognized GDM diagnosed using the National Diabetes Data Group (NDDG) criteria and compared them to 64 nondiabetic controls. The study suggests that unrecognized GDM increases the risks for neonatal complications. The major limitation of the study is the small sample size; the results could have been affected by both alpha and beta errors.

The Toronto Tri-Hospital Gestational Diabetes Project⁷⁶ explored pregnancy outcomes for the 3637 subjects without a diagnosis of GDM whose caregivers were blinded to the OGTT results. There was a direct relationship between OGTT results and a number of adverse pregnancy outcomes, i.e., cesarean delivery, neonatal macrosomia, and preeclampsia. Multivariate analysis was used to control for potential confounding effects; the OGTT results continued to have a significant independent impact. Li et al.⁷⁷ randomly assigned 209 women into three groups based on the OGTT results. The first group “mild GDM” ($n = 75$) based on NDDG criteria was untreated. The second group, GDM, diagnosed after a 75 g OGTT by WHO criteria, was treated. The third group was normal, nondiabetic controls. The results showed a

Table 20.4 The rate of large infants in untreated gestational diabetes

	Macrosomia (%) (≥4000 g)	LGA (%) (≥90th percentile)	Subjects
O’Sullivan et al. ³⁶	15	30	$n = 259$
Coustan et al. ⁹¹	41	47	$n = 34$
Coetzee et al. ⁹²	32	55	$n = 22$
Li et al. ⁷⁷	7	29	$n = 73$
Hod et al. ⁹³	22	34	$n = 32$
Langer et al. ⁷	17	29	$n = 555$
Sermer et al. ⁹⁴	—	35	$n = 150$
Adams et al. ⁷⁵	44	44	$n = 16$
Ostlund et al. ⁷³	33	25	$n = 211$
Landon et al. ⁹	14.3	14.5	$n = 473$
Crowther et al. ⁸	21	22	$n = 510$

significantly higher rate of LGA, 29% in the untreated group (NDDG criteria) when compared to the nondiabetic controls. Neither the women nor caregivers were blinded to the OGTT results, thus allowing the women to initiate dietary and other lifestyle modifications that could potentially have affected glycemic control while leaving the caregivers exposed to a potential labeling bias. Increased morbidity in untreated GDM was demonstrated in several studies (Table 20.4).

There is a wide range of research designs on a continuum from pilot studies to the venerated quasi-randomized,⁷⁸ randomized, and blinded RCT. Randomized and quasi-randomized controlled trials are sometimes necessary if an intervention cannot be blinded. In the past decade, studies utilizing either randomized or case-control design definitively established GDM as a clinical entity and the efficacy of treatment. However, although the RCT is the gold standard, it cannot always be the design of choice since it is contraindicated from an ethical standpoint. For example, if women with even mild GDM are clinically treated, then not treating them for purposes of randomization in a study poses a potential ethical dilemma. Then a realistic and ethical approach is the use of case-control design. As a rule, a well-executed retrospective study has fewer methodologic limitations than a poorly performed prospective study.

Case-control studies are generally a survey study of one point in time. Generally they are descriptive about prevalence or behavior, i.e., prevalence of smoking in pregnancy. This type of study design is quick and relatively inexpensive. The strengths of this format are the potential to study rare events for their antecedent associations as well as its usefulness to generate hypotheses for a prospective study. The weakness of this design is the necessity to match the control to the case study within the same time frame (the common denominator). If not, there is a significantly greater chance for bias in selecting the controls. Finally, a major drawback is the difficulty to show causality.

We,⁷ in the largest to date case-control study, described perinatal outcomes in treated versus untreated GDM that

Table 20.5 Intensified versus conventional management of gestational diabetes mellitus

	Conventional	Intensified	Untreated
Macrosomia (%)	13.6	7.01	16.8
LGA (%)	20.1	13.1	29.4
Metabolic complication (%)	13.3	3.1	29.0
Respiratory complication (%)	6.2	2.3	12.0
Shoulder dystocia (%)	1.4	0.4	2.5
Stillbirth (per 1000)	3.6	1.0	4.2
Cesarean section (%)	22.0	15.0	23.7
Subjects	1316	1145	555

Abbreviation: LGA, large for gestational age.

addressed many of the limitations posed by the aforementioned studies. A population of 555 women with untreated GDM were matched with 1110 women treated for the disease as well as 1110 normal subjects. Patients in the untreated group were recruited to the study after 37 weeks gestation that left the fetus exposed to the glucose toxicity throughout pregnancy and precluded lifestyle modifications such as diet that could have influenced pregnancy outcome. The diagnostic criteria used in the study are one of two accepted and recommended in the last decade since it was supported by two international workshops on GDM that represent international consensus,^{79,80} American College of Obstetricians and Gynecologists (ACOG),⁸¹ and the ADA recommendations.⁸² Two nondiabetic controls were matched to each untreated GDM on the basis of the following characteristics: ethnicity, parity, gestational age at delivery (within 1 week), disease severity (based on fasting plasma glucose level), obesity (BMI), and number of prenatal visits. The treated subjects used self-monitoring blood glucose memory reflectance meters seven times daily in order to receive accurate feedback regarding glycemic profile.

A composite adverse outcome comprised of LGA, neonatal respiratory disease, hypoglycemia, hyperbilirubinemia, shoulder dystocia, and stillbirth enabled the evaluation of neonatal disease (morbidity) in addition to specific morbidity components. A composite adverse outcome of the aforementioned variables was present in 59% of the untreated compared with 18% of the treated and 11% for the nondiabetic population. The rates of LGA infants were 29% in untreated versus 11% with treatment that was similar to the rate in the control population. There was a twofold to fourfold increased risk for large infants and shoulder dystocia, a twofold to sevenfold increased risk for metabolic and respiratory complications, a fourfold increased risk for NICU admissions, and a twofold increased risk for c/s. Multiple logistic regression analysis confirmed fasting glucose as the most predictive cause for the composite perinatal outcome in untreated GDM. There was a twofold to threefold decrease in adverse outcome with treatment after controlling for maternal weight, parity, and disease severity according to fasting glucose level. Moreover, when the outcome in the untreated group was compared to

the GDM group treated by the conventional approach, the results were comparable. In contrast, the pregnancy outcome in GDMs treated with intensified therapy showed significantly lower rates of complications. This finding demonstrates that outcome of pregnancy is directly dependent on treatment modality (Table 20.5).

Fasting plasma glucose is accepted as the gold standard for severity of diabetes. This is true in individuals with type 2 diabetes and in women with GDM. In an attempt to control for different GDM severity levels in the treated and untreated GDMs, we stratified the patients based on increases in fasting plasma glucose (10 mg increments) for each severity category. In the treated GDMs, similar perinatal outcome exists for all fasting severity categories reiterating the importance of achieving targeted levels of glycemic control. In contrast, in the untreated GDMs, significant morbidity was found in each fasting plasma category of severity. Logistic regression revealed in the untreated group that fasting plasma glucose (severity of disease) had a significant independent impact when each 10 mg increment increased the likelihood of adverse outcome (composite) by 15%; for each pound increase in obese patients, the likelihood of adverse outcome increased by 3%. For the treated GDMs, parity was found to have a 6% increment for every child and obesity and weight gain had a negligible effect although both were found to be statistically significant.

Even in patients with lesser degrees of glucose intolerance (fasting plasma glucose <96 mg/dL), there were significantly higher rates of morbidity in untreated women. For the nondiabetic group, the analysis revealed that gestational age at delivery, previous macrosomia, and glucose screening results had significant independent effects on the composite outcome. Moreover, for the mild GDM group (fasting glucose level <96 mg/dL), treatment was associated with 10% LGA rate in comparison to 20% without the benefit of treatment, composite outcome of 31% compared to 17%, respectively. Glucose intolerance discovered during pregnancy can be ameliorated with medical intervention in all levels of GDM severity.

Nearly 40 years have passed from the original O'Sullivan randomized study³⁶ that demonstrated that women

with GDM are at higher risk for macrosomia (13.1% in untreated vs. 4.3% in treated subjects). The ACHOIS randomized study⁸ published in 2005 demonstrated the benefits of treatment of GDM patients. The authors used 75 g OGTT result of 2-hour glucose level between 7.8 and 11 mmol/L (140–198 mg/dL) and fasting plasma <7.8 mmol/L (<140 mg/dL). Blood glucose was monitored 4×/daily with a target fasting value of 3.5–5.3 mmol/L (63–99 mg/dL). Twenty percent of the subjects required insulin therapy to achieve targeted levels of glycemic control. However, the authors failed to report glycemic data and the relationship between glucose levels and pregnancy outcome. The treated group was associated with a significant reduction in the rate of the composite outcome (perinatal death, shoulder dystocia, and birth traumas including fractures or nerve palsy) resulting in an adjusted RR, 0.33; C.I., 0.14–0.75. Secondary neonatal outcomes demonstrated a significantly higher rate in LGA infants in the untreated group compared to the treated group (22% vs. 13%). There were significant increases in NICU rate (71% treated vs. 61% untreated) but did not demonstrate significant differences in the rate of hypoglycemia (defined as requiring intravenous therapy), jaundice (phototherapy), and respiratory complications (supplemental oxygen). In addition, the rate of preeclampsia was 18% in the untreated versus 12% in the treated group.

Both the NICHD and AICHOS studies made significant contributions to the study of GDM. However, the rate of adverse outcome in each of these studies are not comparable. There were different inclusion criteria; the NICHD used fasting plasma glucose <95 mg/dL, while the AICHOS study recruited patients at all levels of the glucose spectrum up to <140 mg/dL (from mild to severe GDM and type 2 diabetes). Additionally, the primary outcome (composite) was different in each study because each contained different variables. In contrast, the previously described case-control study⁷ used the same inclusion criteria as the AICHOS study of fasting plasma <140 mg/dL resulting in similar rates of univariant adverse outcomes. The components in each of the composite outcomes in each of the three studies were dissimilar, and therefore, the rates of composite outcome were not comparable. However, the similarity in all three studies in LGA and macrosomia rates demonstrates that case-control studies can result in comparable results to those in randomized studies when designed appropriately.

Mild untreated hyperglycemia

Another component of the GDM debate surrounds the parameters of the lower threshold of the disease. This element affects the controversy surrounding the diagnostic criteria that has evolved in the past few years from the International Diabetes Study Group based on the HAPO study to the ADA, ACOG, and WHO criteria. The association between mild hyperglycemia and adverse neonatal outcome has been a major concern for the past two decades especially for patients who could not reach the “gold standard” currently used for screening and diagnosis (WHO, NDDG, ADA).

Table 20.6 Association between mild hyperglycemia (OGTT) and fetal macrosomia

	Year	Definition	%LGA	Criteria
Tallarigo et al.	1986	Normal	28	NDDG
Oats et al.	1986	Impaired	22	WHO
Langer et al.	1987	1 abnormal	34	NDDG
Langer et al.	1989	1 abnormal	24	NDDG
Li et al.	1987	Impaired	28	WHO
Herman et al.	1988	Normal	24	NDDG
Lindsay et al.	1989	1 abnormal	18	C&C
Neiger et al.	1991	2 values	21	C&C
Jensen et al.	2001	Normal	21	DPSG-U
Landon et al.	2009	Normal	15	C&C

Many cases in the nondiabetic population may remain unrecognized and, therefore, resulted in untreated GDM with glucose toxicity. They are reinstated into the “normal” population in most maternal clinics; we deliver them every day. This group of patients may unwittingly “contaminate” the rates reported for the normal population by increasing the adverse pregnancy outcome (Table 20.6).

The scientific rationale for the use of two or more abnormal values is not based on evidence but rather on opinions. The explanation for those who support two abnormal values range from “just because” to “better reproducibility of the test.” However, data supporting these positions are lacking. If at all, the existing data suggest that one abnormal value has the same characteristics and predictive value as two or more values. The use of one abnormal value for GDM diagnosis is further supported by the fact that many obstetricians will use screening values of 180 mg/dL or greater as a single diagnosis for GDM and will treat based on this single result.

We, in 1987, suggested, in a case-control study, that women with one abnormal value on the OGTT results have a significantly increased risk for adverse pregnancy outcome when compared to nondiabetic women and women with treated GDM (two or more abnormal values on the OGTT).⁸³ In a follow-up study, women with one abnormal value were randomized into treatment and nontreatment and compared to nondiabetic subjects. The incidence of large infants was significantly higher in the untreated group. When patients were stratified into obese and nonobese for each study group (treated, untreated, and control), there was a significantly higher rate of large infants and metabolic complications in the untreated group. There was no significant difference in the rate of LGA between obese and nonobese patients.⁸⁴ In a third study, we compared the incidence of LGA infants in relation to the number of abnormal values on the OGTT. We found a similar rate of LGA infants when one, two, or three values were abnormal. This was especially true in patients with poor glycemic control.⁸⁵ Similar findings by Lindsay et al.⁸⁶ showed 18% LGA in his study population when one abnormal value was used. Neiger et al.⁸⁷ showed that women

with one abnormal value retested after 4 weeks showed that about 33% had at least two abnormal values on the OGTT. Gruendhammer et al.⁸⁸ studied 152 women with one abnormal glucose value match controlled to 304 nondiabetic women with normal OGTT values. They found that women with only one abnormal OGTT value had increased risk in comparison to the control subjects. Similar results were found in other studies.^{89,90} Recently, the use of one abnormal value as part of GDM diagnosis was endorsed by the International Diabetes in Pregnancy Group and the American Diabetes Association.^{11,82} This endorsement documented that mild to severe hyperglycemia when unrecognized and untreated caused higher rates of adverse pregnancy outcome.

The NICHD Maternal-Fetal Medical Units (MFMU)⁹ trial sought to identify the lower end of the glucose spectrum ("mild" GDM, fasting plasma glucose below 95 mg/dL). The rationale for addressing this end of the spectrum was also related to the ethical considerations of participation in a randomized study of GDM treatment. By following this reasoning, they recognized that patients with abnormal OGTT results (fasting plasma glucose >95 mg/dL) are GDM and, therefore, should be treated. Four hundred and eighty-five women who met the entry criteria were randomized to treatment, and 473 received the standard prenatal care. The treatment arm performed daily self-monitored blood glucose testing with the glycemic target achieved in the vast majority of cases. The primary perinatal outcome was composite outcome that included perinatal death, neonatal hypoglycemia, hyperbilirubinemia, elevated cord C-peptide level, and birth trauma. Secondary

outcome variables were macrosomia (≥ 4000 g), LGA, and neonatal FFM. Maternal outcomes included preeclampsia, induction of labor, and cesarean delivery. The rate of composite outcome in the treated and untreated groups was 32.4% versus 37.0% (nonsignificant), respectively. None of the individual frequency components of the composite outcome were statistically different between the two groups. In the secondary outcomes, there were significantly lower rates of LGA, macrosomia, and shoulder dystocia (1.5% treated vs. 4.0% untreated). Preeclampsia results showed 8.6% for the treated versus 13.6% for the untreated subjects.

There are several major dissimilarities in the research design of each study: the NICHD, AICHOS, and Langer. These variances resulted in different outcome rates. What is more scientifically sound is to indicate and emphasize the direction, i.e., reduced or increased rather than frequency of rates when describing outcomes (Table 20.7). The ACHOIS study⁸ was based on an ethnically homogeneous population, while the NICHD and our study were more ethnically diverse (Langer study more Hispanic women included). The ethnic diversity affects GDM prevalence. In contrast, successful treatment resulted in controlling abnormal glucose levels, which in turn led to lowering the adverse pregnancy outcome. Therefore, treatment will not be affected by ethnicity but rather by achieving targeted levels of glycemic control. As noted earlier, each study used different definitions for composite outcome and metabolic complications (hypoglycemia, hyperbilirubinemia), therefore making study results difficult to compare (Table 20.8).

Table 20.7 Perinatal outcome: In untreated gestational diabetes mellitus

	Langer et al. ⁷	Crowther et al. ⁸	Landon et al. ⁹
Inclusion criteria (fasting)	<140 mg/dL C and C	<140 mg/dL WHO	<95 mg/dL C and C
Composite not comparable	Yes	Yes	Yes
Race or ethnic group (%)			
White	11.0	78.0	25.2
Black	3.0	—	11.4
Hispanic	86.0	—	56.0
Asian and others	—	22.0	7.4
Composite outcome (%)	59.0	4.0	37.0
Macrosomia (%)	16.8	21.0	14.3
LGA (%)	29.4	22.0	14.5
Ponderal index % (>2.85)	22.0	—	—
Metabolic complication (%)	29.0	14.0	28.3
Respiratory complication (%)	12.0	4.0	2.9
Shoulder dystocia (%)	2.5	3.0	4.0
NICU admission (%)	24.0	61.0	11.6
Stillbirth (1000)	5.4	5.7	0.0
Cesarean section (%)	24.0	32.0	33.8
	<i>n</i> = 555	<i>n</i> = 524	<i>n</i> = 473
Abbreviation: C and C, Carpenter and Coustan.			

Table 20.8 Comparison of treatment effect for different outcome definitions in the case-control study, ACHOIS study, and NICHD MFMU trial

	Langer et al. ⁷	Crowther et al. ⁸	Landon et al. ⁹
Inclusion criteria (fasting)	<140 mg/dL C and C	<140 mg/dL WHO	<95 mg/dL C and C
Composite not comparable	Yes	Yes	Yes
Composite outcome	Reduced	Reduced	No difference
Macrosomia	Reduced	Reduced	Reduced
LGA (%)	Reduced	Reduced	Reduced
Metabolic complication	Reduced	No difference	No difference
Neonatal hypoglycemia	Reduced	No difference	No difference
Neonatal hyperbilirubinemia	Reduced	No difference	No difference
Respiratory complication (%)	Reduced	No difference	No difference
Shoulder dystocia (%)	Reduced	No difference	Reduced
NICU admission (%)	Reduced	Increased	Reduced
Stillbirth (1000)	No difference	No difference	0.0
Preeclampsia	No difference	Reduced	Reduced
Induction of labor	Reduced	Increased	No difference
Cesarean section (%)	No difference	No difference	Reduced
	<i>n</i> = 555	<i>n</i> = 524	<i>n</i> = 473

Abbreviation: C and C, Carpenter and Coustan.

Summary

Considering the metabolic heterogeneity of women with GDM and thus their likely broad range of perinatal risk, it is not surprising that descriptions of GDM have ranged from “a major health problem” to “a diagnosis still looking for a disease.” We and others addressed the question of GDM as a clinical entity and the benefits of treating

individuals with GDM that could have a significant impact on the provision of obstetrical care. GDM, when not treated, is associated with increased adverse outcome in pregnancy. Treatment and achievement of targeted levels of glycemic control will result in perinatal outcome comparable to that in the general population. Perinatal outcome and long-term complications for millions of mothers and their offspring are at stake.

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21 Gestational diabetes mellitus in multiple pregnancies

Matteo Andrea Bonomo and Angela Napoli

Epidemiology of multiple pregnancies

Multiple gestations: An epidemic

A true “epidemic” of multiple gestations^{1,2} has been recorded over the last two decades: the 2014 *Practice Bulletin of the American College of Obstetricians and Gynecologists* (ACOG)³ reports that in the United States, the rate of twin births increased 76% between 1980 and 2009, from 18.9 to 33.3 per 1000 births (Figure 21.1). These impressive rises concerned not only simple twin pregnancies. Mainly as a consequence of the spread of assisted reproductive technology (ART) procedures, the rate of triplet and higher-order multifetal gestations rose more than 400% during the 1980s and 1990s, peaking at 193.5 per 100,000 births in 1998, followed by a modest decline to 153.4 per 100,000 births by 2009.³

Despite this partial reversal, reflecting the reduction in the number of embryos transferred with in vitro fertilization (IVF) and the larger numbers of multifetal pregnancy reduction procedures, the most notable feature remains the increased incidence in twin gestations. This has been attributed largely to two concomitant reasons: an older parturient population resulting from delayed childbearing and the rise in use of infertility therapies.^{4,5} Among women attempting conception, the rate of infertility treatment is now estimated at 11%, equally distributed between 5.4% ART procedures and 5.5% ovulation.² This general trend is seen, though with obvious differences, in almost all developed countries.

Twining rates by ethnics and geographical area

Ethnicity seems to play a role in the frequency of multifetal gestations. As reported in the National Vital Statistics Report 2013, among the three largest racial/origin groups in the United States, the multiple-birth rates in 2011 were as follows: non-Hispanic white 38.3‰ (36.6 twins + 1.71 triplets or higher order), non-Hispanic black 38.3‰ (37.2 + 1.1), and Hispanic 23.9‰ (23.1 + 0.8). This also helps explain the differences between different U.S. regions. Multiple-birth rates ranged widely by state, with the highest in New Jersey and the lowest in New Mexico.⁵

Outside the United States, data extracted from the New Zealand medical records of 4939 deliveries, with discharges between 1994 and 1995, reported 1.1% of twin pregnancies, with no differences on an ethnic basis (Europeans 1.2%, Maori 0.8%, Pacific Islanders 1.4%, others 0.4%). The numbers were too small to look at the risk of gestational diabetes mellitus (GDM) within ethnic groups, but the groups were well matched for this.⁶

In Europe, the incidence of twinning rates shows a gradual decrease from north to south. The frequency of multiple pregnancies is high among “Anglo-Saxons,” and even higher in Scandinavia^{7,8}; in contrast, the rate is medium among Slav populations and low for Latins (although data are scanty for Mediterranean areas).^{9,10} In Italy, the rate of spontaneous multiple deliveries in 2010 was 1.6%, ranging from 1.0% to 3.1% (Figure 21.2), with no significant differences between the north, center, and south.¹¹

In East Asian countries, twin maternities are rare; for instance, in Japan the twinning rate has varied between 3 and 9 per 1000 from the 1920s to the 1990s. The patterns of twinning rates in Singapore and Hong Kong are comparable to Japan, though slightly higher.¹⁰

Risk factors

Maternal age

Older women with lower parity are much more likely to give birth to twins or triplets, so the rate of multifetal pregnancies rises with maternal age. As reported in the *ACOG bulletin*, the multiple-birth rate in the United States rises from 16.3 per 1000 live births for women younger than 20 years to 71.1 per 1000 for women 40 years and older.³ A similar relation with age has been reported in Europe. Eriksson et al. found a steady increase in multiple pregnancies starting around 1980, with a marked rise in the age-specific rate in the group aged 40+ years in England and Wales in 2007,⁷ and in Sweden a few years before.⁸ The same was reported by Pison in France and in other western developed countries.⁹ There are probably numerous reasons for these increases. Hypothetically, premenopausal mothers might have hyperstimulation by

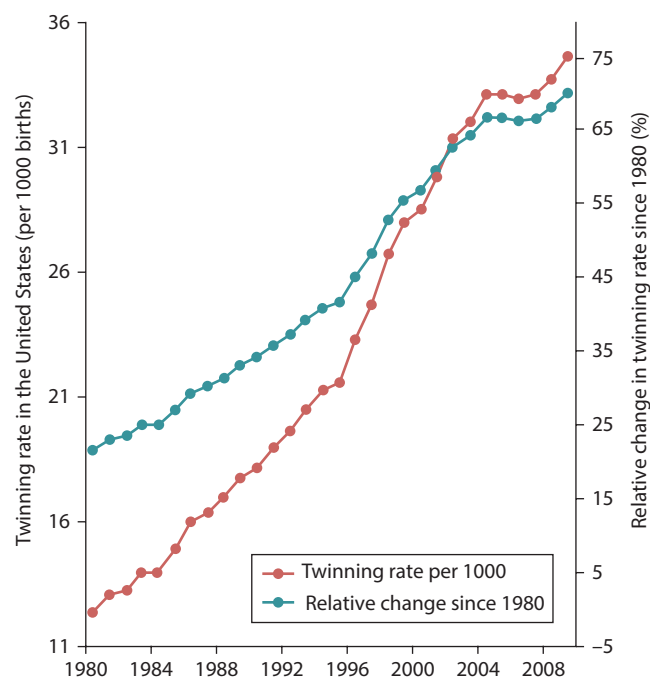


Figure 21.1 Temporal trends and changes in twinning rates in the United States, 1980–2009. (From Ananth, C.V. and Chauhan, S.P., *Semin. Perinatol.*, 36, 156, 2012. With permission.)

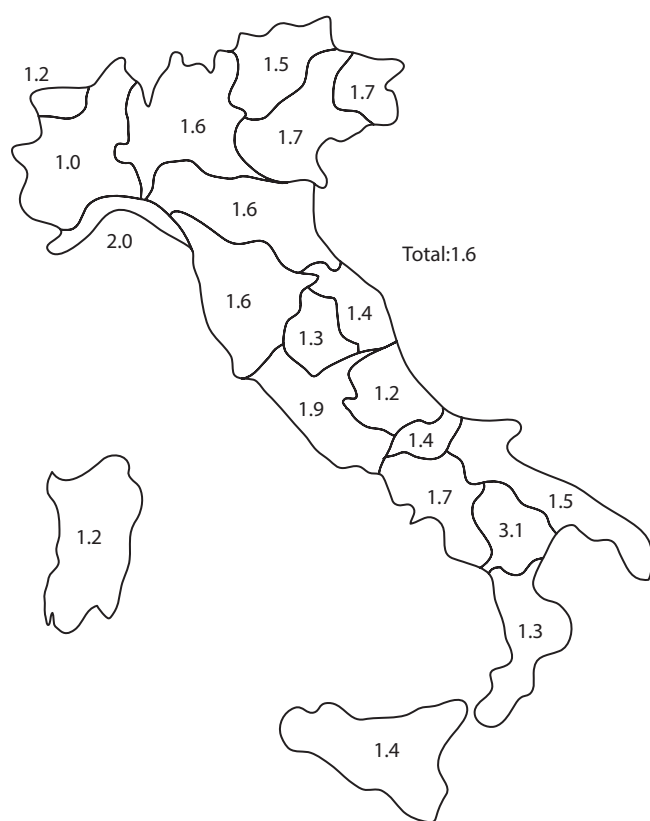


Figure 21.2 Twinning rates (%) in Italy, 2010: regional differences. (Data from Basili, F. et al., *Analisi dell'evento nascita – Anno, 2013, 1, 2010.*)

endogenous follicle-stimulating hormones (FSH) caused by neuroendocrine, hypothalamic, or pituitary mechanisms.²

Assisted reproductive therapy

Infertility therapies influencing the rate of multiple pregnancies include ART procedures (mainly IVF and related procedures) and controlled ovarian hyperstimulation with gonadotropins.^{12,13} Fertility treatments are complex, and each ART cycle consists of several steps that include hormonal treatments to trigger and stimulate the growth of multiple ovarian follicles, medications to suppress the natural menstrual cycle and downregulate the pituitary gland, drugs to bring about final maturation of the eggs (ovulation triggering), and endometrial preparation for placing the embryos in the uterus. Finally, the luteal phase support involves several options including progesterone, estrogen (E2), and human chorionic gonadotropin.

Multiple stimulation regimens are therefore possible, including clomiphene alone, human menopausal gonadotropin (HMG), clomiphene plus HMG, FSH, pulsatile gonadotropin-releasing hormone (GnRH), and FSH plus HMG. The use of GnRH agonists and antagonists has improved pregnancy rates by preventing natural ovulation. Although these approaches influence the maternal endocrine milieu differently, published reports do not usually specify the type of protocol adopted.

According to the most recent report from the National Center for Chronic Disease Prevention and Health Promotion,¹⁴ among 4,046,553 infants born in the United States in 2010, 59,119 (1.5%) were conceived with ART procedures done in 2009 and 2010. Although 96.5% of total infants born in 2010 were singletons, only 53.6% of all ART infants were. Nationwide, 46.4% of ART infants were multiples, compared with only 3.4% of all infants; looking at high-order multiple pregnancies (triplets or higher), the frequency after ART procedures was 3.0%, compared with only 0.1% of all infants. Overall, in 2010, 19.2% of all twin and 32.5% of triplet or higher-order births in the United States were conceived with ART.

These treatments in women who on average are older and weigh more may further influence the maternal hormone concentrations in pregnancies that are often multiple.¹⁵

Physiology of multiple pregnancies

Weight and caloric intake

Given the increased metabolic rate and higher caloric needs in twin pregnancies, the U.S. Institute of Medicine Guidelines established specific nutritional and weight guidelines.¹⁶ Women with a twin gestation and normal body mass index (BMI) are recommended to gain 37–54 lb (17–24 kg), overweight women 31–50 lb (14–22 kg), and obese women 25–42 lb (11–19 kg). The daily recommended caloric intake for women with normal BMI who are pregnant with twins is 40–45 kcal/kg during the first trimester, then adjusted as necessary for the weight gain goal.¹⁷

Table 21.1 Twin pregnancy nutritional recommendations: Micronutrients

Micronutrient supplement (daily total intake)	First trimester	Second trimester	Third trimester
MVI with iron (30 mg elemental tablet)	1	2	2
Calcium (mg)	1500	2500	2500
Vitamin D (international units)	1000	1000	1000
Magnesium (mg)	400	800	800
Zinc (mg)	15	30	30
DHA/EPA (mg)	300–500	300–500	300–500
Folic acid (mg)	1	1	1
Vitamin C (mg)	500–1000	500–1000	500–1000
Vitamin E (international units)	400	400	400

Source: Modified from Goodnight, W. et al., *Obstet. Gynecol.*, 114, 1121, 2009. With permission.
Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MVI, multivitamin.

Iron and other micronutrients

Women with twin gestations require nearly double the iron replacement (about 869 mg elemental iron) of a singleton pregnancy, on account of the larger amount being transported to the fetuses. When iron-deficiency anemia is manifest, 60–120 mg of elemental iron daily for 4 weeks raises the hemoglobin concentration by 1 g/dL. Considering the increased incidence of hypochromic anemia already present in twin pregnancies, appropriate iron supplementation is strongly indicated in these women, as both in singleton and multiple pregnancies it can reduce the 3–17 times higher risk of requiring blood transfusion during cesarean section because of mild-to-severe preoperative anemia as well as the risk of premature labor and the severity of postpartum hemorrhage.^{18,19}

Recommendations for micronutrient supplementation in twin pregnancies, summarized in Table 21.1, are based on expert opinion, and the long-term implications for a woman's health due to nutrient deficiency are not known. However, calcium, vitamin D, zinc, magnesium, folate, vitamin C, and omega-3 fatty acids are all important in fetal development.¹⁸

Glycemic homeostasis in pregnancy

Singleton pregnancy: A potentially diabetogenic condition

Pregnancy itself is to some extent a “diabetogenic” state on account of the continuous changes in maternal hormone concentrations. Over the course of gestation, the insulin response to nutrients progressively rises, while glucose tolerance changes only slightly. The balance is maintained by progressive increases in basal and postprandial insulin concentrations to counteract the rising insulin resistance.²⁰ At the end of pregnancy, the basal and 24 hours mean insulin concentrations may be double those before pregnancy, with the first and second phases of insulin secretion three times greater.^{20–22}

The increases in insulin resistance mean slightly higher postprandial concentrations of metabolic fuels including

glucose, lipids, and amino acids are available for the fetus. Even with hepatic glucose production increased by approximately 30%, fasting glucose concentrations fall, probably secondary to the fetoplacental utilization. Placental and fetal demand for glucose is considerable and may even approach the equivalent of 150 g/day of glucose in the third trimester.

Glucose transport to the fetus is in direct proportion to the maternal levels and is boosted by a fivefold increase in placental glucose flux even in the absence of maternal hyperglycemia. If fetal glucose requirements cannot be met because of maternal hypoglycemia or placental insufficiency, the fetus can draw on alternate substrates, such as ketone bodies derived from beta-oxidation of fatty acids.

Insulin does not cross the placenta, and fetal insulin production starts early.

Multiple pregnancy: A potentially diabetogenic condition

Women with multifetal gestations undergo significant physiological adaptations beyond the metabolic, cardiovascular, and hematologic changes expected for a singleton pregnancy. The levels of pregnancy-related diabetogenic hormones, including human placental lactogen, estrogens, progesterone, and cortisol,²³ are higher in multiple than singleton pregnancies because of the growing placental mass. At term, the median weight of twin placentas is about 1119 g, almost double the median placental weight for singleton boys (679 g) and girls (668 g).²⁴

Although the larger placental mass in twin gestation results in an increase in placental-derived steroid hormones that may predispose to glucose intolerance by increasing insulin resistance, the risk is likely to be offset by the increase in caloric expenditure with the higher metabolic rate necessary to maintain a twin/multiple gestation.²⁵ Twin gestations have higher metabolic rates than a singleton pregnancy, with maternal resting energy expenditure 10% greater, resulting in a 40% increase in caloric requirements.¹⁷ In addition, BMI and weight gain during pregnancy, which are important contributors to the insulin resistance, are also higher in twin than singleton pregnancies.^{26–29}

Gestational diabetes

Glycemic goals

Glucose control is essential during pregnancy for mothers with diabetes and their infants, as the risks for adverse health outcomes and quality of life correlate with maternal glucose levels. There are no specific recommendations on glycemic goals in twin diabetic pregnancies, but recent research suggests weekly self-monitoring blood glucose (SMBG) + HbA1C provides more complete data for glucose control during pregnancy, as SMBG alone can miss certain high glucose values.³⁰

Multiple pregnancies and GDM

Diagnosis

Considering the various differences between twin and singleton pregnancies, one might assume that the accuracy and characteristics of the diagnostic tests would differ too. Surprisingly, however, data in support of this hypothesis are limited and not concordant.³¹

In a retrospective study of 2554 Italian women screened for gestational diabetes, Corrado et al. found that twin gestation was independently associated with an increased risk for an abnormal 50 g glucose challenge test (GCT) result. However, the positive predictive value (PPV) of an abnormal GCT for gestational diabetes was lower in twin gestations, as the overall rate of GDM was similar in singleton and twin pregnancies.³²

Similarly, in a multiethnic population, Simmons et al. reported that women with twin pregnancy had higher 1-hour GCT results, but not significantly higher rates of positive GCT. In the small numbers of women with an oral glucose tolerance test (OGTT), the incidence of GDM was not significantly higher than in singleton pregnancies. However, as the significantly wider screening for GDM among women with twin pregnancies (77.8% vs. 50.6%) should have reduced the difference in GDM risk, these authors concluded that twin

pregnancies were more prone to GDM.⁶ Therefore these women should be screened again in late pregnancy too.

Yogev compared the performance of the 50 g GCT in 529 twin and 14,268 singleton pregnancies followed at a single center in Israel, through the Clalit Health Services database.³³ This study comprises one of the largest cohorts in a single center addressing the issue of the GCT in twin pregnancies. The authors found that women with twin pregnancies were approximately twice as likely to have an abnormal GCT and were also more likely to have a normal OGTT than women with singleton pregnancies (Tables 21.2 and 21.3). Women in the twins group had higher mean GCT results (104.7 ± 28 vs. 98.5 ± 25 mg/dL, $p < 0.001$), more GCT results higher than 130 mg/dL (20.2% vs. 11.8%, $p < 0.001$) (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.7–2.7) or GCT >140 mg/dL (13.8% vs. 9.6%, $p = 0.001$) (OR 1.9, 95% CI 1.5–2.5) even after adjustment for maternal age, parity, and fetal sex. The PPV for a GCT >140 mg/dL was significantly lower in the twins group for either one or more or two or more abnormal values in the OGTT (Table 21.3). The overall rates of GDM, when diagnosed with CGT >200, were similar in the twin and singleton groups (3.0% vs. 3.6%).

Although these were all retrospective studies, with no information on potential confounders, the 50 g GCT appears to give a higher false-positive rate and a lower PPV in twins than singleton pregnancies, since a mild form of glucose intolerance does not translate into a difference in the rate of GDM. Some authors suggest that the diabetogenic effect resulting from the rising levels of placental hormones is partially counteracted by the increased glucose demand due to the presence of multiple fetuses and the higher basal metabolic rate.²⁵

Frequency of gestational diabetes in twin pregnancies

Few studies have examined the risk of GDM in women carrying multiple pregnancies, and their findings are conflicting. This could be partially due to differences in the criteria for diagnosing GDM (World Health Organization,³⁴ Australasian Diabetes in Pregnancy Society ADIPS,³⁵

Table 21.2 Common screening tests for gestational diabetes mellitus in twin pregnancies

Author ^{ref} (country)	Study	Year	50 g GCT Twin versus singleton (no.)	Abnormal GCT Twin versus singleton (%)	OGTT+ after GCT + (≥140 mg/dL) Twin versus singleton (%)
Corrado ³² (Italy)	Retrospective Single center	2003	70 versus 2,484	31.4 versus 20.0	18.1 versus 16.1, NS
Simmons ⁶ (New Zealand)	Retrospective Multicenter Multiethnic	2002	54 versus 4,885	17.9 versus 12.6	50 versus 28.3, NS
Yogev ³³ (Israel)	Retrospective Single center	2014	529 versus 14,268	13.8 versus 9.6	OGTT ≥1 <i>abnormal result</i> 21.1% versus 33.8% $p = 0.03$ ≥2 <i>abnormal results</i> 12.7% versus 23% $p = 0.04$

Abbreviation: GCT, glucose challenge test.

Table 21.3 OGTT results in twin and singleton pregnancies with an abnormal glucose challenge test result (>140 mg/dL)

Outcome	Twins (71)	Singletons (1222)	p value
Mean gestational week at testing	27.2 ± 1.7	27.5 ± 2.6	0.3
Result 1 (fasting)			
Mean (mg/dL)	75.0 ± 11.7	75.2 ± 14.5	0.9
>95 mg/dL	2 (2.8)	74 (6.1)	0.3
Result 2 (60 min)			
Mean (mg/dL)	160.0 ± 33.9	162.0 ± 31.8	0.6
>180 mg/dL	13 (18.3)	338 (27.7)	0.09
Result 3 (120 min)			
Mean (mg/dL)	129.3 ± 30.7	128.7 ± 29.5	0.9
>155 mg/dL	11 (15.5)	229 (18.7)	0.5
Result 4 (180 min)			
Mean (mg/dL)	93.6 ± 15.8	97.3 ± 21.2	0.1
>140 mg/dL	3 (4.2)	47 (3.4)	0.7
No abnormal results (false-positive GCT)	56 (78.9)	809 (66.2)	0.03
One or more abnormal results	15 (21.1)	413 (33.8)	0.03
Two or more abnormal results	9 (12.7)	281 (23.0)	0.04

Source: Modified from Yogeve, Y. et al., *J. Matern. Fetal. Neonatal Med.*, 27, 57, 2014. With permission.
Note: Results are presented as mean ± SD, or no. (%).
Abbreviation: GCT, glucose challenge test.

National Diabetes Data Group,³⁶ and Carpenter and Coustan,³⁷ as well as to the small populations studied and differences in study design).

The oldest studies, in the 1980s, used an i.v. glucose tolerance test to evaluate the carbohydrate metabolism, but the results in twin and singleton pregnancies were not univocal.^{23,38,39} Subsequently, however, with the OGTT, some studies have indicated an increase in the incidence of GDM in twin pregnancies,^{31,40–42} while others find no difference from singleton pregnancy rates^{43–45} (Table 21.4). In the United States, a retrospective cohort-based analysis of 281,505 twin births between 1995 and 2000 confirmed a 3.5% rate of diabetes⁴⁶; mothers were more likely to be black (6.9% vs. 3.8%) and older than 35 (28.8% vs. 18.5%). Unfortunately, there

was no information on the clinical subtypes of diabetes in pregnancy. However, during the study reference period, universal screening for GDM was in place. The 3-hour 100 g OGTT was routinely used for the diagnosis of GDM, according to the diagnostic criteria recommended by the American Diabetes Association or the National Diabetes Data Group.

The actual role of multiple pregnancies in the frequency of GDM is also hard to establish because of the confounding effect of ART and other infertility treatments that, as we have seen earlier, often give rise to multifetal pregnancies. Many recent studies report higher rates of GDM in pregnant women treated with various types of ART or ovarian hormonal stimulation; this finding, however, was seen both in singleton and multiple pregnancies, suggesting a direct effect

Table 21.4 Prevalence of gestational diabetes mellitus in singleton and multiple pregnancies, based on oral glucose tolerance test

Author ^{ref}	Study	Year	No. pregnancies Multiple/singleton	Diagnostic criteria	% GDM Multiple/singleton	p value
Naicker ⁴⁵	Case control	1983	26/26	Response to GTT 50 g	Glucose similar response	NS
Wein ⁴¹	Retrospective	1992	798/61,914	WHO	7.4/5.6	0.012
Henderson ⁴⁴	Case control	1995	130/130	NDDG	5.8/5.4	NS
Roach ⁴⁰	Retrospective	1998	71/824	ADIPS AU	15.5/9.1	<0.001
Schwartz ³¹	Retrospective	1999	429/29,215	NDDG	7.7/4.1	<0.05
Simmons ⁶	Retrospective	2002	54/4,885	ADIPS NZ	11.9/5.1	0.05
Buhling ⁴³	Case/control	2003	89/178	C&C	3.4/3.4	NS
Rauh-Hain ⁴²	Retrospective	2008	553/22,503	NDDG	4.0/2.3	0.01

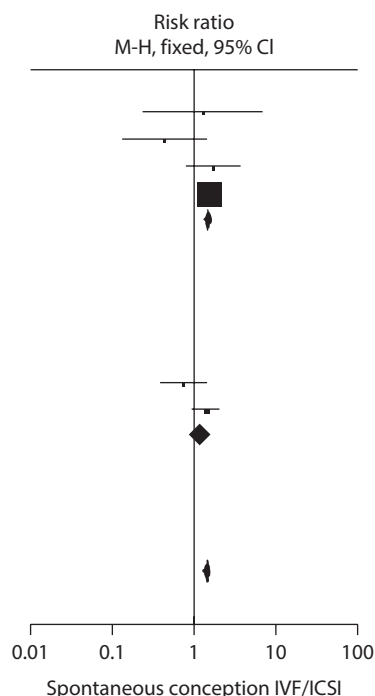


Figure 21.3 Relative risk of gestational diabetes in assisted reproductive technology compared with spontaneous single-ton conceptions. (From Pandey, S. et al., *Hum. Reprod. Update*, 18, 485, 2012. With permission.)

of these therapies on glucose tolerance in pregnancy, separate from their part in multifetal gestations. A meta-analysis of obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI, by Pandey and colleagues, was published in 2012⁴⁷; in six studies reporting GDM, regarding 13,399 pregnancies,^{48–53} the relative risk of GDM after ART procedures was 1.48 compared with spontaneous conception (Figure 21.3). It is worth noting that the higher risk persisted in subgroups of matched cohort studies and when sensitivity analysis was done only in good-quality studies.

Other studies in recent years^{54–56} mostly confirm the higher risk of GDM in singleton pregnancies with ART. Of particular interest is the article by Wang et al. on a retrospective cohort of more than 400,000 pregnancies registered

between 2007 and 2009 in the Australian National Perinatal Data Collection.⁵⁷ Comparing ART and non-ART pregnancies, the overall frequency of GDM was significantly higher in the ART group (7.6% vs. 5.0%). Looking then at multiple pregnancies, even though the prevalence of GDM was higher in ART than non-ART cases, multivariate analysis did not show a significant difference (Table 21.5).

These data suggest that the higher risk of GDM after ART is not due to an effect on multifetality and that other factors must be considered—for example, the cause of infertility.

GDM metabolic management in multiple pregnancies

Considering the high prevalence of twin pregnancies, and the frequency of GDM in these mothers, it is surprising and disappointing that there is so little data on the best metabolic approach to multiple pregnancies complicated by glucose intolerance. Only one study, by Schwartz et al., published in 1999 in *American Journal of Obstetrics and Gynecology* (AJOG),³¹ addressed this question in detail. They examined the obstetric database of the Detroit Medical Center–Sinai Hospital between January 1, 1990, and June 30, 1998. In about 30,000 deliveries, GDM was found in 1222 (4.1%) of singleton and 33 (7.7%) of twin pregnancies. Both the proportion of women requiring insulin and the average daily insulin doses were only minimally higher in twin than singleton GDM pregnancies (30.3% vs. 24.4% and 67.8 U [units] vs. 56.2 U, respectively, NS [not significant]). Fasting and 2-hour postprandial SMBG were also similar in the two groups, well below the therapeutic target values, set at 100 mg/dL in the fasting state and 120 mg/dL 2 hours after meals.

Other studies also report no differences in the therapeutic approach to GDM in singleton and multiple pregnancies,⁵⁸ at least for twins; higher-order multiple pregnancies might present different, more serious problems, due to the larger placental mass resulting in higher production of placental-derived hormones that may lead to greater insulin resistance and, consequently, metabolic alterations. No studies are available, however, on metabolic control in GDM complicating triplets and up, probably because of the small numbers—although they are not so rare any more in most developed countries.⁵⁹

Table 21.5 Prevalence of gestational diabetes mellitus in pregnancies conceived with assisted reproductive technology procedures, compared with spontaneous conception (nonassisted reproductive technology)

	Non-ART		ART		OR (95% CI)	AOR ^a (95% CI)
	Total (no.)	GDM (%)	Total (no.)	GDM (%)		
All mothers	386.660	5.0	13.732	7.5	1.53 (1.43–1.64)	1.26 (1.18–1.36)
Singleton	381.402	7.3	12.105	8.8	1.22 (0.99–1.49)	1.18 (0.94–1.48)
Twin	5.208	5.0	1.571	7.6	1.55 (1.45–1.65)	1.28 (1.20–1.37)

Source: Modified from Wang, Y.A. et al., *Hum. Reprod.*, 28(9), 2554, 2013. With permission.

Note: Data from the Australian National Perinatal Data Collection (NDPC), 2007–2009.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

^a Adjusted for age, parity, body mass index, health insurance, smoking during pregnancy, and essential hypertension.

Coming back to simple twin GDM pregnancies, probably the period of metabolic derangement after diagnosis (few weeks) is too short to make it necessary to introduce significant changes in the therapeutic approach usually adopted in singleton pregnancies complicated by the same problem. This is not true, however, for twin pregnancies in mothers who already have type 1 diabetes.

In a retrospective study of 15 twin pregnancies with type 1 diabetes followed at the same center in Copenhagen, Callesen and colleagues⁶⁰ investigated the insulin requirement during gestation, compared with a group of 108 singleton pregnancies with type 1 diabetes. With a HbA1c target $\leq 5.6\%$ in the second part of pregnancy, they reported small increases in insulin doses from prepregnancy until 8 weeks, a decrease from 8 to 14 weeks, a substantial increase from 14 to 27 weeks, and a stable insulin requirement from 27 to 33 weeks. Thus, the insulin requirement before pregnancy until 14 weeks was comparable in twin and singleton pregnancies; the total insulin requirement increase doubled weekly between 14 and 27 gestational weeks in twin pregnancies; this was explained by the growth of the total fetal and placental mass. From 27 to 33 weeks, the insulin requirement remained fairly stable compared with the continuous steady rise usually seen in singleton diabetic pregnancies; this was very likely due to the more limited placental and fetal growth often seen toward the end of twin pregnancies, possibly associated with some stagnation in hormonal production, although the final placental weight was 74% higher in twins than singleton pregnancies with type 1 diabetes (1220 vs. 700 g).

As placental growth can be expected to follow similar patterns in twin pregnancies with GDM, the smaller increase in insulin needs in these women might conceivably be attributable to a lower degree of glycometabolic alteration, and to its shorter duration, insufficient to cause a substantial difference from singleton pregnancies.

Glucose control and pregnancy outcome

GDM generally raises the risks of adverse complications for both mother and child,^{61,62} but these risks can be reduced with appropriate diagnosis and treatment.^{63–65} Pregnancies complicated by untreated or suboptimally controlled GDM

present high rates of hypertensive disorders and preeclampsia,⁶⁶ and the most frequent perinatal complications are excessive fetal growth and macrosomia,⁶⁷ with consequent increased frequency of birth trauma, shoulder dystocia and maternal morbidity due to operative delivery, and preterm deliveries. Perinatal mortality rates (stillbirths and neonatal death) may also be higher than normal.

On the other hand, as reported in Table 21.6, a twin or multiple pregnancy is itself a risk factor for several perinatal negative outcomes,^{18,68,69} such as low birth weight (LBW) and prematurity,⁷⁰ stillbirth and neonatal death,^{71–73} maternal hypertension and preeclampsia, and hemolysis, elevated liver enzymes, and low platelets syndrome.^{74,75} It is therefore interesting to see how the combination of these two potentially dangerous conditions—GDM and twin pregnancy—influence pregnancy outcomes. The few studies reported in the last decade have produced controversial results.

A small group of 28 twin pregnancies with GDM was examined in 2003 by Moses et al. in Australia⁷⁶ in comparison with 29 control twin normoglycemic pregnancies; no differences were found in pregnancy outcome (birth weight, Apgar score, gestational week of delivery), with the exception of a higher rate of elective cesarean sections for twin pregnancies.

In 2006, a Korean group⁷⁷ examined 99 twin pregnancies delivered at Cheil General Hospital in Seoul in 1998–2002, in a case–control study comparing 33 women with GDM and 66 nondiabetic mothers. Again, no significant differences were found in birth weight, Apgar score, respiratory distress syndrome, and other possible complications such as meconium aspiration pneumonia, transient tachypnea of newborn, hyperbilirubinemia, hypoglycemia, hypocalcemia, and congenital anomalies. Intrauterine fetal death occurred in two pregnancies in each group (NS). Women with GDM were followed with a glycemic target of 60–95 mg/dL fasting, and 120 mg/dL 2 hours postprandial; insulin (added when at least 20% of measurements were above the target) was necessary in 6 out of 33 (18%) cases, achieving optimal glucose control in all cases.

Three other studies have since been published on the same subject: in 2011 in Portugal by Simões,⁷⁸ in 2012 by González González⁷⁹ in nine tertiary university centers in

Table 21.6 Obstetric and perinatal complications in multiple pregnancies

Outcome	Singleton	Twins	Triplets	Author ^{ref}
Birth weight <1500 g (%)	1.1	9.8	35.3	Martin ⁵
Birth weight <2500 g (%)	6.3	56.3	94.4	Martin ⁵
<32 weeks gestation (%)	1.6	11.3	36.5	Martin ⁵
<37 weeks gestation (%)	10.0	57.3	93.4	Martin ⁵
Cerebral palsy (‰ live births)	1.6	7.0	28.0	Petterson ⁷¹
Infant mortality (‰ live births)	5.4	23.6	52.5	Luke ⁶⁸
Maternal hypertensive disorders (%)	6.5	12.7	20.0	Day ⁷⁵
HELLP syndrome	0.2	0.9	2.1	Day ⁷⁵

Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelets syndrome.

Spain, and in 2013 by Luo et al.,⁴⁶ using 1995–2000 data of the U.S. National Center for Health Statistics (NCHS).

Simões et al.⁷⁸ reported a retrospective case–control study on 105 twin pregnancies with GDM matched, with a 3:1 ratio, with 315 non-GDM controls. The only significant difference was in the prevalence of respiratory distress at birth and jaundice, which were more frequent in GDM pregnancies; a higher rate of perinatal mortality in the same group did not reach statistical significance. No information was available on the glucose control in diabetic mothers.

The Spanish group conducted a retrospective observational study on 534 twin pregnancies, 257 with GDM and 277 with normal glucose tolerance.⁷⁹ GDM was associated with a higher risk of hypertensive complications, prematurity, and macrosomia (not large for gestational age [LGA]), but a significantly lower risk of small-for-gestational-age (SGA) infants. Prematurity was related not to GDM but to other pregnancy complications. Apgar scores, rate of admission to neonatal intensive care units, and perinatal mortality were similar in mothers with GDM and controls.

The study by Luo et al.⁴⁶ is important because of the huge number of pregnancies examined. From the NCHS matched multiple-birth data for 1995–2000, the authors obtained information on about 20,000 twin pregnancies complicated by diabetes (the type of diabetes was not specified, but probably mainly GDM), and more than 540,000 nondiabetic twin pregnancies. A previous article by the same group⁸⁰ had reported a potential protective effect of diabetes against neonatal death in twin pregnancies. Therefore, to exclude the hypothesis that this apparently positive result could “mask” serious problems preceding delivery causing an increase in fetal deaths, this study was designed to assess the consequences of diabetes complicating twin pregnancies on perinatal mortality, considering both fetal and neonatal deaths. The results, however, were not univocal: the risks of stillbirths and neonatal death were lower in very preterm or very-low-birth-weight twin diabetic pregnancies, but not among neonates with normal birth weight, where these rates were higher in diabetic women. Moreover, the lower risk of perinatal death in diabetic twin pregnancies was observed for vaginal but not cesarean section births. Overall, however, perinatal death was less frequent in twin diabetic than nondiabetic pregnancies (2.1% vs. 3.3%), confirming the trend evidenced in 2011.

Looking at secondary outcomes, in diabetic pregnancies, mothers were more likely to have reported any other maternal major illness (10.6% vs. 4.6%) or to have a cesarean section delivery (60.8% vs. 51.9%). Preterm (61.4% vs. 56.1%) or LGA (13.3% vs. 9.3%) births and congenital anomalies (2.8% vs. 2.1%) were also more frequent in diabetic pregnancies. Extremely preterm births were slightly less frequent (10.5% vs. 12.1%) and slightly preterm births more frequent (50.9% vs. 44.0%) in diabetic pregnancies. LBW (52.5% vs. 54.6%) and SGA (9.9% vs. 10.8%) infants were slightly less frequent in diabetic pregnancies. Among the extreme preterm births in diabetic and nondiabetic pregnancies, SGA was slightly less frequent (10.0% vs. 11.7%), while LGA was similar (10.1% vs. 9.7%). Given the higher rates of twin pregnancy

complications and patient or provider preference, there were 2.5 times the number of cesarean sections compared with singleton deliveries.

Discussion and conclusions

The substantial increase in the frequency of multiple pregnancies recorded in the last few decades, mainly as a result of the growth in the use of ART techniques and therapies linked to ovarian stimulation, led us to expect some negative consequences related to the potential “diabetogenic” effect of the growing placental mass. There was worry not only about an increase in the prevalence of GDM and other alterations in the carbohydrate metabolism in these cases, but also about unfavorable outcomes in women with both these independent risk factors—GDM and multiple pregnancy.

In actual fact, the figures on the prevalence of GDM in multiple pregnancies are discordant. There does appear to be a greater frequency of minor glucose tolerance disorders, particularly with frequently positive 50 g OGTT, but there seems to be no rise in the diagnoses of GDM. There may in fact, therefore, be some sort of compensatory effect, resulting from the greater calorie consumption and higher metabolic rate, which would reduce the consequences on the material carbohydrate metabolism of the altered endocrine *milieu* due to the high concentrations of placental hormones with “anti-insulin” action.

Similarly, in women with GDM complicating a multiple pregnancy, the obstetric and perinatal outcomes seem no different from single pregnancies. This obviously depends on how metabolic control is maintained after diagnosis, but it does not seem any harder to manage diabetes during a multiple pregnancy. The proportions of women requiring insulin are in fact close to those for single pregnancy, and the insulin doses needed in such cases do not seem any higher; the situation is different, however, in multiple pregnancies with pregestational diabetes.

There even seems to be a protective effect against perinatal mortality, at least for preterm births and very-low-birth-weight neonates, as if slight hyperglycemia in early pregnancy gave some sort of “survival advantage.” Luo’s findings, however, are surprising and certainly call for further confirmation, with greater details of the type of metabolic alteration present.

In conclusion, the question of how GDM and multiple fetuses are related is definitely important, especially in view of the current “epidemic” of multiple pregnancies. However, findings so far on the interaction between the two conditions seem reassuring. Once more, the main factor is the importance of metabolic control on the outcome of a pregnancy complicated by GDM, so it is essential to achieve and maintain optimal glycemic levels, regardless of the number of fetuses. Diagnostic and therapeutic strategies regarding the carbohydrate metabolism in women with multiple pregnancies should therefore be no different from the universally accepted approach for single pregnancies, which have achieved progressive improvements in maternofetal outcomes in recent years.

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22 Glycemic goals in diabetic pregnancy and defining “good control”: Maternal and fetal perspective

Liran Hirsch and Yariv Yogeve

Introduction

The association between diabetes during pregnancy and the risk of adverse maternal and fetal outcome is well established. Maternal complications include spontaneous abortions, preterm deliveries, preeclampsia, nephropathy, cesarean section, and among others birth trauma. The main fetal and neonatal complications are congenital anomalies, deviant fetal growth, birth-related trauma, metabolic abnormalities, and stillbirth. Moreover, evolving evidence indicate that diabetes, among other components of the metabolic syndrome, is a significant risk factor for childhood and adult obesity and cardiovascular disease, due to in utero programming mechanisms including altered organ development, cellular signaling responses, and epigenetic modifications of gene expression.¹⁻⁴

Not only that improving glycemic control reduces the risk for adverse outcome in pregestational diabetes,^{5,6} but also in gestational diabetes mellitus (GDM), treatment and achieving desired level of glycemic status effectively diminishes the risk for complications.⁷⁻⁹ Yet several issues should be addressed when discussing the relation between glycemic control and adverse pregnancy outcome. First, how is good glycemic control defined? What is the glucose threshold that should be reached in order to diminish the risk for adverse outcome? Second, is maintaining glycemic control according to the recommendations and guidelines can truly abolish the increased risk for complications as compared to the general population? Finally, how glucose status should be monitored during pregnancy in regard to the methods used, diurnal occasions, and frequencies?

Glucose thresholds and perinatal complications

Several authoritative bodies have recommended varying levels of glycemia that need to be targeted in pregnant patients with diabetes. The sources of these recommendations utilized the concept of isolated normality based on nondiabetic glucose profiles and are usually well-defined cutoff levels.¹⁰⁻¹² Yet, it appears that one cannot address glucose as a dichotomous variable but as a continuous one, with type of complications and rate depending upon the level of glycemic control. The association between glycemic control and several main perinatal complications will be further discussed in the following paragraphs.

Perinatal mortality

The most devastating adverse fetal outcome is perinatal mortality. However, since congenital anomalies, which are also important complications of maternal diabetes, are a major contributing factor in the overall perinatal mortality rate, it is important to adjust for the effect of congenital malformations when calculating fetal and neonatal death rates. Karlsson and Kjellmer evaluated the effect of the degree of maternal glycemia (expressed as the mean daily blood glucose value) on perinatal mortality in 179 women with pre-existing diabetes.¹³ Patients were divided into three groups with the following mean blood glucose: <100, 100–150, and >150 mg/dL. Perinatal mortality was 3.8%, 16%, and 24%, respectively, although no correction was made for congenital anomalies. Yet these data suggest that strict glycemic control (<100 mg/dL) is necessary for diminishing the risk for

perinatal mortality in this population. However, perinatal mortality rate is increased not only in women with preexisting diabetes but also in women with GDM.^{14–16} In GDM, the effect of other factors, such as the relatively older pregnant mother in comparison to the gravid nondiabetic population and the presence of comorbidities (e.g., hypertension, obesity), may also attribute to the increased risk of perinatal death. In a large cohort study of 4,757 women with GDM and 10,804 nondiabetic gravidas, the rate of perinatal mortality was evaluated.¹⁷ In this cohort, 79% of the study population achieved targeted levels of glycemic control (mean blood glucose < 105 mg/dL). The incidence of stillbirth was 4.8/1000 for the subjects with GDM and 4.2/1000 for the nondiabetic subjects with neonatal death rates of 5.2/1000 and 5.3/1000, respectively. It seems that achievement of targeted levels of glycemic control in the GDM population can reduce the perinatal mortality to rates comparable to the general population. Similar rates of perinatal mortality between nondiabetic gravidas and patients with intensified managed GDM were reported.¹⁸ This study demonstrates again the relative protective effect of controlling the abnormal levels of glycemia.

The data suggest that both gestational and preexisting diabetes are associated with increased perinatal mortality when established level of glycemia is not achieved. Although the increased rate for perinatal mortality may be multifactorial, it appears that a threshold of mean blood glucose <100–110 mg/dL will be sufficient for the prevention of this complication.

Congenital anomalies

Since GDM is expressed in the late second or early third trimester, which is beyond the period of fetal organogenesis, congenital anomalies are a complication of mainly preexisting diabetes. In studies reporting the association between glycemic control and congenital anomalies, the method that was used for glycemic control evaluation was hemoglobin A1C (HbA1C), mean blood glucose, mean fasting glucose, or mean postprandial glucose levels depending upon the study.^{19–22} Temple et al., in a study measuring HbA1C, found an increased rate of congenital anomalies already in threshold of 7.5% (1% vs. 8%, $p = 0.03$), which translates to mean blood glucose of approximately 170 mg/dL.¹⁹ Others, who used glucose profile to define the threshold for anomalies, suggested fasting plasma glucose of <120 mg/dL, postprandial <140 mg/dL, preprandial <120 mg/dL, and overall mean <110 mg/dL.^{22–24} In these studies, the preconception rate of anomalies was 1%–1.5%, and in patients above these thresholds, the rate of anomalies ranged from 6% to 12%. With regard to congenital anomalies, the critical period for intervention and risk reduction is before or early in gestation making preconceptional care mandatory.²⁵

Deviant fetal growth: Macrosomic and growth-restricted fetuses

In the general population, the rate of macrosomia (≥ 4000 g) is 8%–10%, and the rate of large-for-gestational-age (LGA)

infants based on its mathematical definition (>90th percentile) is 10%. Similarly, the rate of small-for-gestational-age (SGA) infants (<10th percentile) should be 10%. The rates found in those of pregnant diabetic women should, therefore, be compared to the aforementioned baselines. Previous studies have reported rates of macrosomia and LGA of 10%–20% and 15%–30%, respectively.^{26–29} However, when exploring the association between the level of glycemic control and fetal growth pattern, a control should be made for important confounding variables that were proven to be associated with neonatal over-/undergrowth such as maternal obesity, gestational weight gain, and preeclampsia.^{30–32}

Numerous studies have shown that by achieving the desired glycemic control, the rate of macrosomia and LGA of neonates among diabetic gravidas can be reduced to closer, if not similar, to the general population.^{18,33–35} Landon et al. reported an LGA rate of 9.3% with a mean blood glucose <110 mg/dL in 43 patients with well-controlled type 1 diabetes.³⁵ With mean blood glucose levels >126 mg/dL in 32 patients, the LGA rate was 34%. Langer and associates found a rate of LGA in women with preexisting diabetes comparable to the rate in the general population (10%) when the mean self-monitoring blood glucose (SMBG) was within 90–95 mg/dL.¹⁸ In a secondary analysis of the Metformin in Gestational Diabetes (MiG) trial evaluating 724 women with GDM who failed to achieve desired glycemic control under exclusive diet therapy, the lowest risk for LGA was when mean fasting glucose value was <90 mg/dL and when 2-hours postprandial values were <105–115 mg/dL unrelated to maternal body mass index or treatment modality.²⁹

However, it appears that tighter is not always better. Langer et al.³⁶ have found that in GDM a threshold of mean blood glucose <87 mg/dL was associated with an increased risk for SGA neonates. Similar relationship was found between lower HbA1C levels before delivery (<5.7%) and increased risk for SGA infants in women with type 1 diabetes.²⁸ Thus, in respect to deviant fetal growth patterns, both upper and lower threshold should be used to define desired glycemic control.

Metabolic abnormalities and respiratory complications

Metabolic complications include fetal hypoglycemia, polycythemia, hyperbilirubinemia, and hypocalcemia. The main contributor to metabolic complications is fetal hyperinsulinemia, which is also responsible for fetal macrosomia. Thus, it is reasonable that the recommended thresholds for macrosomia prevention will likewise be advisable for metabolic complications. Studies in women with type 1 diabetes reported that a mean blood glucose <110 mg/dL was associated with a significant reduction in rates of neonatal hypoglycemia and respiratory complications compared to poorly controlled gravidas¹³ and that the rates were comparable to the nondiabetes population.³⁵ In GDM, good glycemic control (mean fasting glucose < 95 mg/dL and either 1 hour postprandial <140 mg/dL or 2 hour postprandial <120 mg/dL) was associated with decreased rates of neonatal hypoglycemia (7.1% vs. 9.3%, $p = 0.031$) compared to those who did

not reach good glycemic control.³⁷ Langer et al. found that mean blood glucose <100 mg/dL was associated with similar rates of metabolic complications in gravidas with GDM compared to nondiabetic controls, and that higher levels were associated with up to eightfold increased risk.³⁸ As regards to respiratory complications, mean blood glucose >106 mg/dL was associated with delayed appearance of biochemical markers of pulmonary maturity, though without correlation with clinical neonatal respiratory morbidity.³⁹ In contrast, others failed to demonstrate the relation between glycemic control and appearance of biochemical markers of pulmonary maturity,^{40,41} except for uncontrolled diabetes (mean glucose >120 mg/dL) at preterm.⁴⁰

Preterm delivery

Preterm delivery is considered the most important etiology for neonatal morbidity and mortality. There is a comparable incidence of preterm delivery in women with pregestational diabetes between types 1 and 2 diabetes (33.6% in women with type 1 vs. 32% in women with type 2).⁴² According to a multicenter survey (435 pregnancies in women with pregestational diabetes), diabetes was directly implied in preterm delivery risk particularly when first trimester HbA1C >8% occurred and in cases of preexisting nephropathy.⁴³ Others reported that the risk of delivering preterm was more than 40% when HbA1C was above 7.7% in week 8.⁴⁴ In a study of 253 gravidas with pregestational diabetes, those with spontaneous preterm delivery had at delivery higher mean HbA1C levels ($8.1\% \pm 1.4\%$ vs. $7.4\% \pm 1.2\%$, $p = 0.002$) and blood glucose (148 ± 30 vs. 109 ± 24 mg/dL, $p = 0.043$) compared to those delivered at term.⁴⁵ However, there are differing opinions if GDM as a single indicator increases the risk of preterm delivery. Several authors have suggested that there was a higher incidence of preterm delivery in association with different levels of glucose intolerance,^{46–48} while others found no difference in the rate of preterm delivery in comparison to the nondiabetic population.^{49,50} Scarce data, however, exist regarding the effect of maternal glycemic control and the risk of preterm delivery. Bar-Hava et al.⁴⁹ demonstrated in a small study similar overall rates of preterm delivery in both subjects with GDM ($n = 34$ women) and without GDM ($n = 68$ women). Moreover, women with GDM who delivered at term or preterm had similar glycemic profiles for both the entire treatment period and the week preceding delivery. In contrast, in a large study ($n = 1526$), Yogev et al.⁴⁸ reported that the mean blood glucose was independently associated with the risk for spontaneous preterm delivery in women with GDM (odds ratio [OR] of 1.94, confidence interval [CI] 1.25–3.02) and that only 35% of women with spontaneous preterm delivery have reached the desired glycemic control (defined as mean blood glucose <105 mg/dL) compared to 54% in those delivered at term ($p = 0.004$). It seems that in pregestational diabetes, HbA1C level <7.7%–8% in early gestation is desired for the prevention of preterm delivery, whereas mean blood glucose of <105–110 mg/dL could alter the risk of preterm delivery in both gravidas with GDM and with pregestational diabetic.

Preeclampsia

Although many studies have reported an increased risk for hypertension and preeclampsia among women with diabetes,^{42,51–54} some have disputed this relationship.^{55,56} In women with pregestational diabetes, Cohen et al. found that first-trimester HbA1C levels were higher in those who subsequently developed preeclampsia compared to those who did not (7.7% vs. 6.7%, $p = 0.001$).⁵⁷ The association between high HbA1C levels (>8%) during early pregnancy and the rate of subsequent preeclampsia was further reported by others.⁶ These findings further emphasize the importance of prepregnancy optimization of glycemic profile in women with type 1 and 2 diabetes. The association between glycemic control and the rate of preeclampsia was also reported in women with GDM. Yogev et al. found in 1183 women with GDM that those with mean blood glucose <95 mg/dL had similar rates of preeclampsia regardless of the severity of GDM (defined by fasting blood glucose levels on the oral glucose tolerance test).⁵⁴ However, in women with mean blood glucose >95 mg/dL, the rate of preeclampsia was higher in those with fasting glucose >115 mg/dL compared to <115 mg/dL (18.0% vs. 9.8%, OR 2.56, 95% CI 1.5–4.3). In addition, the severity of GDM (OR 1.7, 95% CI 1.21–2.38) was independently and significantly associated with an increased risk of preeclampsia.⁵⁴ Others found that fasting glucose levels >90 mg/dL and/or 2-hour postprandial levels >120 mg/dL were associated with increased risk for preeclampsia (OR 8.40, 95% CI 4.57–15.42, $p < 0.001$).⁵⁸

In summary, the level of glycemic control in women with pregestational diabetes and GDM is associated with increased risk for maternal and neonatal complications. However, glucose values are best described as a continuous variable, and the risk to the fetus increases in direct relation to the increased level of maternal glycemia. In addition, the risk for each outcome measure was shown to correlate with different glucose threshold. Thus, even if optimal glycemic goals cannot be reached, it is important to keep on struggling as it would still minimize the risk for complications even if not abolish it.

Recommended glucose thresholds and normal glucose values during pregnancy: Are they the same?

Various glycemic thresholds were recommended in patients with diabetes complicating pregnancy (Table 22.1).^{10,59–61} Although not identical, the cutoff levels proposed by the different authoritative bodies for each diurnal occasion are within a 10–15 mg/dL range. For example, while the American College of Obstetricians and Gynecologists have recommended fasting levels of 60–90 mg/dL,¹⁰ the *Fifth International Workshop-Conference on GDM* recommended fasting glucose level <95 mg/dL.⁶⁰ However, the sources of these recommendations utilized the concept of “mimicking” normality as they were based on nondiabetic

Table 22.1 Comparison between recommended glycemic thresholds in pregnancy and glycemic profile of nondiabetic gravidas

	Recommended glycemic thresholds				Glycemic profile in nondiabetics
	American College of Obstetrics and Gynecologists ¹⁰	American Diabetes Association ⁵⁹	Fifth International Workshop-Conference on GDM ⁶⁰	Canadian Diabetes Association ⁶¹	Yogev et al. ⁶²
Fasting (mg/dL)	60–90	<105	<96	<95	75 ± 12
Premeal (mg/dL)	60–105	GDM <95/type I or II DM—60–99	—	—	78 ± 11
Postmeal (mg/dL)					
1 hour	<130–140	<155	<140	<140	105 ± 13
2 hours	<120	<130	<120	<120	97 ± 11
Mean (mg/dL)	100	—	—	—	84 ± 18

Abbreviations: DM, diabetes mellitus; GDM, gestational diabetes mellitus.

glucose profiles. One of only few studies who reported data concerning glycemic profile in nondiabetic gravidas was conducted by Yogev et al., who measured interstitial glucose levels in subcutaneous tissue every 5 minutes using continuous glucose monitoring (CGM) for 72 consecutive hours in nondiabetic gravidas.⁶² They found that for nonobese women, the fasting blood glucose level was 75 ± 12 mg/dL, the mean blood glucose level was 83.7 ± 18 mg/dL, the postprandial peak glucose value level was 110 ± 16 mg/dL, and the time interval that was needed to reach peak postprandial glucose level was 70 ± 13 minutes. A similar postprandial glycemic profile was obtained for breakfast, lunch, and dinner. Obese women were characterized by a significantly higher postprandial glucose peak value, increased 1- and 2-hour postprandial glucose levels, increased time interval for glucose peak, and significantly lower mean blood glucose during the night. No difference was found in fasting and mean blood glucose between obese and nonobese subjects. Almost similar results in nonobese nondiabetic gravidas were obtained by Parretti et al.⁶³ The thresholds endorsed by various authoritative bodies represent merely the upper 1 or 2 standard deviations from mean glucose value of nondiabetic gravidas, while other factors such as maternal BMI or the specific outcome variable, which was meant to be prevented, was not encountered. In addition, even if nondiabetic glucose profile is achieved by a diabetic gravida, is it sufficient for preventing diabetes-associated complications?

Does achieving good glycemic control eliminate complications associated with diabetes?

The management of diabetes in pregnancy, as put forward by the “St. Vincent” declaration, was aimed at achieving near-normal pregnancy outcomes.⁶⁴ However, despite aggressive

research, advances in glucose monitoring, and treatment modalities, women with diabetes complicating pregnancy still experience higher rate of adverse outcome compared to the general population. Several studies have shown that even meticulous glucose control aiming and achieving strict glycemic targets, as advised by present guidelines and recommendations, did not eliminate adverse perinatal outcome, especially macrosomia, compared to the general population. In a small study, the rate of macrosomic fetuses of 14 women with type 1 diabetes who were treated with continuous subcutaneous insulin infusion and reached a desired glycemic control was assessed.⁶⁵ Mean HbA1C level by trimesters was 6.5% ± 0.9%, 5.9% ± 0.7%, and 5.8% ± 0.6%. Yet average birth weight was 3312.1 ± 750 g with macrosomia (>4000 g) rate of 35%. Evers et al. reported similar findings in a cohort of 289 gravidas with type 1 diabetes, of whom 25.3% had a birth weight greater than 4000 g.⁶⁶ The mean HbA1C (%) levels achieved were 6.5 ± 1.0, 6.0 ± 0.9, and 6.2 ± 1.1 during the first, second, and third trimester, respectively. Evidence from studies by Mello et al.⁶⁷ and Howorka et al.,⁶⁸ who showed that mean glucose levels required for normal birth weight was <100 mg/dL with standard deviation (SD) of 12 mg/dL (noting a high rate of hypoglycemia) also supports the argument that macrosomia prevention requires more strict glycemic control than usually recommended during pregnancy complicated by diabetes.

Glucose monitoring: The effect on glycemic control and pregnancy outcome

The ability to monitor glucose values is of historical significance, since throughout recorded history, physicians have been familiar with diabetes and have “finger dipped” in order to detect the “sweetness” of patients’ urine. This imperfect technique was used until the development of urine sticks

in the early twentieth century that were sensitive enough to detect glycosuria. Research efforts have continuously been directed toward the development of a process for testing blood glucose using either visual or electronic interpretation with a reflectance meter. The original meters used a wet method that often required as many as four steps (approximately 10 minutes/step) to obtain one test result. Today's reflectance meters are more user-friendly and include a memory chip for data storage and one-step testing. Recently, a CGM technique was developed that facilitates the collection of even more accurate glucose data. However, is it the most sophisticated method of glucose monitoring associated with the best clinical results?

Glycosylated hemoglobin: Can a single measure of glycemic level be valuable?

Traditionally, in nonpregnant diabetic patients, glycosylated hemoglobin (HbA1C) became the indicator of long-term glycemia. It is a modification of hemoglobin caused by the attachment of glucose to the N-terminus of the beta chain. The rate of attachment is determined by the glucose concentration in the blood. Based on the lifespan of the red blood cells that averages 120 days, different reports have suggested that the predictability of HbA1C ranges from 4 to 10 weeks.^{69,70} Thus, it is virtually impossible to alter treatment modality based on retrospective data, especially in GDM since the window of opportunity is so small. Yet lately, Jovanovic et al. found that in 24 women with GDM and initial HbA1C $\geq 7.0\%$, a decline of 0.47% per week in HbA1C levels was observed in response to carbohydrate-restricted diet or insulin treatment.⁷¹ This finding, if proven by larger-scale studies, could reflect a possible utility of HbA1C measurement during therapy. Until then, HbA1C measurement should be reserved for preexisting diabetes especially at the first office visit for counseling for the risk of congenital anomalies and macro and micro complications throughout pregnancy.

Is there an optimal frequency for blood glucose determinations?

Nowadays, the role of SMBG in nonpregnant and pregnant women has become the standard of care for achieving targeted levels of glycemic control.⁷² However, the optimal frequency for blood glucose determinations is unclear. Langer et al.¹⁸ demonstrated in a prospective study that a mean blood glucose obtained from SMBG (seven times/day, intensified treatment group), using memory reflectance meters, identified more fetal macrosomia and other neonatal morbidities in comparison to weekly fasting and 2-hour laboratory glucose determinations supplemented by four times/day (unverified) self-monitoring with only test strips and no meters. Of note, the compliance in the intensified treatment group was not ideal since the mean test per day was only 5.2 instead of 7 as instructed. Others have reported similar results with four/day glucose determinations as compared to less intensified treatment.⁷³

In patients with type 1 diabetes, Kerssen et al.⁷⁴ reported that the detection of hyper- and hypoglycemia was significantly higher in women with 10 or more SMBG determinations daily than in patients with fewer. However, no correlation with pregnancy outcome was reported. In contrast, Homko et al.⁷⁵ randomly assigned 58 women with diet-controlled GDM and a fasting blood glucose level <95 mg/dL to two groups. The experimental group measured their blood glucose levels four times daily using a reflectance meter with a memory chip. Metabolic status was assessed in the control group by periodic monitoring at prenatal visits. They reported no significant differences with regard to dietary compliance, birth weight, gestational age at delivery, rates of macrosomia, delivery by cesarean section, Apgar scores, and neonatal complications. It seems that the optimal frequency for blood glucose monitoring should probably be different among the various diabetes groups with diet-controlled GDM needing the less frequent monitoring.

The role of continuous glucose monitoring during pregnancy

The main advantage of CGM is by recognizing period of hypo- or hyperglycemia that could not be detected using routine determinations using SMBG. In pregnancies complicated with type 1 diabetes, Yogeve et al.⁷⁶ demonstrated a mean total time (192 ± 28 minutes/day) of undetected hyperglycemia (glucose levels > 140 mg/dL) identified by CGM, which would not be recognized if SMBG was used alone. Moreover, when GDM patients were evaluated, the mean total time of hyperglycemia was 132 ± 31 minutes/day for those treated with insulin and 94 ± 23 minutes/day for those treated with diet only.⁷⁷

The efficacy and effectiveness of CGM during pregnancy was assessed in a recently published systematic review by Voormolen et al.⁷⁸ They retrieved 5032 articles, 11 of which remained as relevant after selection according to predefined criteria. Of those, only two studies were randomized controlled trials (RCTs) evaluating the effect on pregnancy outcome with conflicting results. Murphy et al.⁷⁹ randomly allocated pregnant women with type 1 or 2 DM to either standard antenatal care with SMBG ($n = 33$) or to standard antenatal care with additional CGM use ($n = 38$). Retrospective CGM was planned every 4–6 weeks for a period of 5–7 consecutive days and was executed on average 4.2 times per pregnancy. Lower HbA1C values were seen throughout pregnancy in the CGM group, but this difference did not reach statistical significance until at 32–36 weeks of gestation ($5.8\% \pm 0.6\%$ vs. $6.4\% \pm 0.7\%$, $p = 0.007$). The incidence of LGA was significantly lower in the CGM group with OR for reducing LGA rate of 0.36 (95% CI, 0.13–0.98; $p = 0.05$). Comparison of other outcomes such as mode of delivery and neonatal morbidity was not significantly different. It must be noted that the intervention group included three twin pregnancies and four children with birth weights under the 10th percentile, whereas there were none in the control group ($p = 0.1$). Logically, this affected the mean birth weight of the intervention group for the better, though a

birth weight below the 10th percentile must be considered an unwanted result. In contrast, a high-quality RCT by Secher et al.⁸⁰ randomized 154 women with either type 1 or 2 DM and a singleton pregnancy for the additional use of real-time CGM ($n = 79$) or routine antenatal care with SMBG seven times daily ($n = 75$). The CGM was intermittently planned at 8, 12, 21, 27, and 33 weeks of gestation and was executed at least three times by 75% of the women. Women assigned to real-time CGM had baseline HbA1C similar to that of women in the control arm (median 6.6% vs. 6.8%, $p = 0.67$). At 33 gestational weeks, HbA1C levels remained comparable regardless of the real-time CGM use. The prevalence of LGA infants (45% vs. 34%; $p = 0.19$) and other perinatal outcomes (e.g., preeclampsia, cesarean delivery, preterm delivery, and neonatal hypoglycemia) were comparable between the arms.

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Summary

Maternal hyperglycemia is associated with increased risk for adverse perinatal outcome with no single threshold that eliminates the risk for all adverse outcomes. Yet maintaining glucose level as close to recommended values may minimize the risk for most complications. In addition, it is obligatory that women with type 1 or 2 DM receive proper prepregnancy counseling emphasizing the need for reaching euglycemia prior to conception and close surveillance during gestation. The evolving research regarding the use of continuous glucose monitoring and its effect on glycemic control and pregnancy outcome combined with improvement in pharmacotherapy options will hopefully lead to safer pregnancy for both the mother and fetus.

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23 Insulin therapy in pregnancy

Lois Jovanovic and John L. Kitzmiller

Introduction

Before the advent of insulin, few diabetic women lived to childbearing age. Before 1922, fewer than 100 pregnancies in diabetic women were reported, and most likely these women had type 1 and not type 2 diabetes.¹ Even with this assumption, these cases of diabetes and pregnancy were associated with a >90% infant mortality rate and a 30% maternal mortality rate. As late as 1980, physicians were still counseling diabetic women to avoid pregnancy. This philosophy was justified because of the poor obstetric history in 30%–50% of diabetic women. Improved infant mortality rates finally occurred after 1980, when treatment strategies stressed better control of maternal plasma glucose levels, and once self-monitoring blood glucose (SMBG) and glycosylated hemoglobin (A1C) became available. As the pathophysiology of pregnancy complicated by diabetes has been elucidated, and as management programs have achieved and maintained near-normal glycemia throughout pregnancy complicated by type 1 diabetes, perinatal mortality rates have decreased to levels seen in the general population. This review is intended to help the clinician understand the increasing insulin requirements of pregnancy and to design treatment protocols to achieve and maintain normoglycemia throughout pregnancy.

Glucose toxicity and the role of postprandial hyperglycemia

If the mother has hyperglycemia, the fetus will be exposed to either sustained hyperglycemia or intermittent pulses of hyperglycemia; both situations prematurely stimulate fetal insulin secretion. Fetal hyperinsulinemia may cause increased fetal body fat (macrosomia) and, therefore, a difficult delivery, or cause inhibition of pulmonary maturation of surfactant and, therefore, respiratory distress of the neonate. The fetus may also have decreased serum potassium levels caused by the elevated insulin and glucose levels and may therefore have cardiac arrhythmias. Neonatal hypoglycemia may cause permanent neurological damage. There is also an increased prevalence of congenital anomalies and spontaneous abortions in diabetic women who are in poor glycemic control during the period of fetal organogenesis, which is nearly

complete by 7 weeks postconception. Thus, a woman may not even know she is pregnant at this time. It is for this reason that prepregnancy counseling and planning is essential in women of childbearing age who have diabetes. Because organogenesis is complete so early on, if a woman presents to her health-care team and announces that she has missed her period by only a few days, if the blood glucose levels are immediately normalized, then there is still a chance to prevent cardiac anomalies, although neural tube defects are already “set in stone” by the time the first period is missed. These findings emphasize the importance of glycemic control at the earliest stages of conception.^{2–4} Ideally, if a diabetic woman plans her pregnancy, then there is time to create algorithms of care that are individualized and a woman can be given choices. When a diabetic woman presents in her first few weeks of pregnancy, there is no time for individualization, but rather rigid protocols must be urgently instituted to provide optimal control within 24–48 hours. After the period of organogenesis, maternal hyperglycemia interferes with normal fetal growth and development during the second and third trimesters.⁵ The maternal postprandial glucose level has been shown to be the most important variable to impact on the subsequent risk of neonatal macrosomia.^{6–8} The fetus thus is “overnourished” by the peak postprandial glucose level.⁹ This peak response occurs in >90% of woman at 1 hour after beginning a meal. Therefore, 1 hour after beginning a meal, the glucose level needs to be measured and treatment designed to maintain this blood glucose in the normal range. Studies have shown that if the postprandial glucose levels are maintained from the second trimester onward to <120 mg/dL 1 hour after beginning a meal, then the risk of macrosomia is minimized.⁸

Diabetogenic forces of normal pregnancy increase insulin requirements¹⁰

The fetal demise associated with pregnancy complicated by type 1 diabetes seems to arise from glucose extremes. Elevated maternal plasma glucose levels should always be avoided, because of the association of maternal hyperglycemia with subsequent congenital malformation and spontaneous abortions.^{2,5} To achieve normoglycemia, a clear understanding

of “normal” carbohydrate metabolism in pregnancy is paramount. Thus, the amount of insulin required to treat women with type 1 diabetes throughout pregnancy needs to be sufficient to compensate for (1) increasing caloric needs, (2) increasing adiposity, (3) decreasing exercise, and (4) increasing anti-insulin or diabetogenic hormones of pregnancy. The major diabetogenic hormones of the placenta are human chorionic somatomammotropin (hCS), previously referred to as human placental lactogen, estrogen, and progesterone. Also, serum maternal cortisol levels (both bound and free) are increased. In addition, at the elevated levels seen during gestation, prolactin has a diabetogenic effect.¹⁰ The strongest insulin antagonist of pregnancy is hCS. This placental hormone appears in increasing concentrations beginning at 10 weeks of gestation. By 20 weeks of gestation, plasma hCS levels are increased 300-fold, and by term, the turnover rate is 1000 mg/dL. The mechanism of action whereby hCS raises plasma glucose levels is unclear, but probably originates from its growth hormone-like properties. hCS also promotes free fatty acid production by stimulating lipolysis, which promotes peripheral resistance to insulin. Placental progesterone rises 10-fold above nonpregnant levels and is associated with an insulin increase in normal healthy pregnant women by two- to fourfold. Most of the marked rise of serum cortisol during pregnancy can be attributed to the increase of cortisol-binding globulin induced by estrogen. However, free cortisol levels are also increased. This increase potentiates the diurnal fluctuations of cortisol with the highest levels occurring in the early morning hours. The rising estrogen levels also trigger the rise in pituitary prolactin early in pregnancy. Prolactin's structure is similar to a growth hormone, and at concentrations reached by the second trimester (>200 ng/mL), prolactin can affect glucose metabolism. Although there are no studies that have examined prolactin alone as an insulin antagonist, there is indirect evidence that suppressing prolactin in women with gestational diabetes with large doses of pyridoxine improves the glucose tolerance. In addition to the increasing anti-insulin hormones of pregnancy, there is also increased degradation of insulin in pregnancy caused by placental enzymes comparable to liver insulinases. The placenta also has membrane-associated insulin-degrading activity. Concomitant with the hormonally induced insulin resistance and increased insulin degradation, the rate of disposal of insulin slows. The normal pancreas can adapt to these factors by increasing the insulin secretory capacity. If the pancreas fails to respond adequately to these alterations, then gestational diabetes mellitus (GDM) results. In a woman with type 1 diabetes, her insulin requirement will rise progressively. Failure to increase her insulin doses appropriately will result in increasing hyperglycemia.¹⁰

Rationale for the use of human insulin during pregnancy

Although controversial, the rate of complications in pregnancies of diabetic women has been tied to the metabolic control of maternal glucose.¹⁻⁵ Perhaps the debate remains

because some reports claim that neonatal complications occur in spite of excellent metabolic control, although they fail to measure postprandial glucose levels.^{11,12} Postprandial glucose control has been suggested as a key to neonatal outcome for the pregnant woman with either type 1 diabetes or GDM.⁶⁻⁸ Alternatively, some have suggested that neonatal morbidity is secondary to the variability of maternal serum glucose and the presence of antibodies to insulin.¹³ Placental transfer of insulin complexed with immunoglobulin (Ig) G has also been associated with fetal macrosomia in mothers with near-normal glycemia during gestation. Menon et al.¹³ reported that antibody-bound insulin transferred to the fetus was proportional to the concentration of antibody-bound insulin measured in the mother. Also, the amount of antibody-bound insulin transferred to the fetus correlated directly with macrosomia in the infant and was independent of maternal blood glucose levels. In contrast, Jovanovic et al.¹⁴ discovered only improved glucose control, as evidenced by lower postprandial glucose excursions, but not lower insulin antibody levels, correlated with lower fetal weights. They showed that insulin antibodies to exogenous insulin do not influence infant birth weight. It has been reported that both insulin lispro and insulin aspart (analogs of human insulin with a peak insulin action achieved within 1 hour after injection) significantly improve the postprandial glucose levels in nonpregnant diabetic patients.¹⁵⁻²¹ Because normoglycemia is important in the treatment of pregnant diabetic women, the use of insulin analogs would appear beneficial in the care of these women if the safety profile can be documented. This review presents the reports that studied the safety and efficacy of insulin analogs in pregnancy and offers an opinion as to the utility of insulin analogs for the treatment of the diabetes during pregnancy.

Concern about anti-insulin antibody formation during pregnancy

Anti-insulin antibodies that cross the placenta may contribute to hyperinsulinemia in utero and thus potentiate the metabolic aberrations in the fetus. Although insulin does not cross the placenta, antibodies to insulin do cross and may bind fetal insulin; this necessitates the increased production of free insulin to reestablish normoglycemia. Thus, the anti-insulin antibodies may potentiate the effect of maternal hyperglycemia to produce fetal hyperinsulinemia.

Human and highly purified insulins are significantly less immunogenic than mixed beef-pork insulins.¹⁶ Human insulin treatment has been reported to achieve improved pregnancy and infant outcome compared to using highly purified animal insulins.¹⁴ Insulin lispro (which has the amino acid sequence in the beta chain reversed at positions B28 and B29) has been reported to be more efficacious than human regular insulin to normalize the blood glucose levels in women with GDM. This insulin rapidly lowered the postprandial glucose levels, thereby decreasing the A1C levels, with fewer hypoglycemic episodes and without increasing

the anti-insulin antibody levels.¹⁷ In addition, the safety and efficacy of insulin lispro in the treatment of type 1 diabetes in women throughout pregnancy has recently been reported.²² Also, insulin aspart has recently been reported to be safe and efficacious in type 1 diabetic women.²³ However, there are only case reports and a small series of the use of the long-acting insulin analogs²⁴⁻²⁷ during pregnancy. They appear to be associated with increased macrosomia, however.²⁷ The following discussion helps the clinician decide if the newer insulin's benefit outweighs any risks.

Use of rapid-acting insulin analogs in pregnancies complicated by diabetes

Postprandial glucose control in a patient with GDM is important to neonatal outcome.⁶⁻⁸ The Diabetes in Early Pregnancy (DIEP) study identified 28.5% of infants from diabetic mothers who were >90th percentile in infant birth weights.⁸ The birth weight in this 28.5% correlated positively with fasting blood glucose and A1C. When adjusted for fasting blood glucose and A1C, the nonfasting blood glucose concentration in the third trimester was even a stronger predictor of infant birth weight and fetal macrosomia. Combs et al.⁷ confirmed these findings, as they associated macrosomia with higher postprandial glucose concentrations obtained between weeks 29 and 32 of gestation. In addition, they described a higher risk of small-for-gestational-age (SGA) infants in those with lower (<130 mg/dL [7.2 mmol/L]) 1-hour postprandial glucose levels. DeVeciana et al.⁶ described improved fetal outcome and less risk of neonatal hypoglycemia, macrosomia, and cesarean delivery in patients who managed GDM by controlling 1-hour postprandial glucose concentrations than in those who managed by only the preprandial glucose concentrations. Therefore, rapid-acting insulin analogs that possess unique properties may make it a valuable therapeutic option in the treatment of GDM and the prevention of neonatal complications. First, the rapid absorption of insulin lispro from the subcutaneous site allows for a faster insulin peak concentration versus regular human insulin.^{17,18} This effect more closely mimics the physiologic first-phase insulin release and results in lower postprandial glucose concentrations, and may lead to improved postprandial coverage.¹⁵ In addition, insulin lispro is known to upregulate insulin receptors.^{19,20} In the present authors' study,¹⁷ the postprandial glucose response to the test meal was more frequently within the normal glucose range after a standardized dose of insulin lispro as compared with regular human insulin. Second, the elimination of insulin from the venous space is the same as with regular human insulin, but the faster absorption of insulin lispro allows both the glucose-lowering effect and the patient's exposure to insulin to be less, which may result in a diminished antibody response. Certainly, in clinical trials, there has not been any increase in antibody response associated with insulin lispro use.^{15,18,19,22} Since placental transfer of insulin occurs when it is complexed with Ig, the lack of insulin lispro-induced antibody formation could be expected

to result in little, if any, placental transfer of insulin lispro to the neonate, as was demonstrated in the present authors' study. Thus, the overall decrease in circulating insulin lispro, plus the lower immunogenic response of lispro, leads to less maternal antibody formation and, therefore, less insulin transfer to the fetus with a reduction in the risk for physical malformations.^{17,21} Menon et al.¹³ attempted to link maternal antibody formation to negative fetal outcomes. Careful review of the paper reveals, instead, better overall control of maternal hyperglycemia with attendant reductions in fetal macrosomia. This may have ultimately diminished the risk of neonatal complications, including macrosomia. Previous investigations have demonstrated that birth weight could be normalized with regular human insulin.²²⁻²⁴ This aggressive therapeutic intervention may explain the apparent lack of macrosomia in both patient groups. There are no differences in fetal parameters, as would be expected in the clinical setting where euglycemia is a goal of therapy, which reduce the risk to the fetus. Although the present authors were interested in the metabolic effects of insulin lispro in women with GDM, the primary concern was safety, specifically the risk of hypoglycemia, hyperglycemia, and antibody production that might cause the insulin to cross the placenta to the fetal side. In the study, 42 women with GDM were randomized to receive regular human insulin or insulin lispro prior to consuming a test meal.¹⁷ Throughout the remainder of gestation, subjects received premeal insulin lispro or regular human insulin (with and without basal insulin) and performed blood glucose monitoring before and after each meal. During the test meal, the areas under the glucose curve, and those for insulin and C-peptide levels, were significantly lower in the insulin lispro group. The incidence of postprandial hyperglycemia (>120 mg/dL) was significantly lower in the lispro group. Overall metabolic control also improved significantly in the insulin lispro group, which showed the greatest absolute decrease in A1C levels as compared to the regular human insulin group. The reduction from baseline A1C concentrations at 6 weeks was statistically significant for the insulin lispro group but not for the regular human insulin group.¹⁷ To determine the immunologic effects of insulin lispro compared with regular human insulin, three different types of antibodies were studied: (1) lispro-specific antibodies, (2) regular specific antibodies, and (3) cross-reactive antibodies. Levels of all three antibodies were evaluated at the time of enrollment, at 6 weeks after enrollment, at delivery (both in the maternal serum and the umbilical cord blood), and at the postpartum follow-up visit in maternal serum. No statistically significant differences were seen between the insulin lispro and regular human insulin groups. Now there are several reports of the safety and efficacy of both insulin lispro and insulin aspart in pregnancy to confirm the results of the original report.¹⁷⁻²⁵ Insulin aspart has also been suited in a similar fashion as insulin lispro. Wyatt et al.²² have reported that insulin aspart is not immunogenic, improved the area under the curve for the postprandial glucose excursion, and facilitates term delivery of a healthy infant. In addition, the patient satisfaction was improved using insulin aspart compared to regular human insulin. Conclusions

from these studies are that those women with GDM who are not optimally managed with diet and exercise need insulin therapy. Insulin lispro and insulin aspart cause fewer hypoglycemic events than human regular insulin, and it attenuates a greater postprandial response than regular human insulin. Furthermore, the antibody levels are not increased over those seen with regular human insulin, and therefore, insulin lispro and insulin aspart may be considered a treatment option in patients with GDM.

Theoretical risks of the use of insulin analogs during pregnancy complicated by pregestational diabetes

Diamond and Kormas²⁸ first questioned the safety of using insulin lispro during pregnancy in 1997. They reported on two patients who used insulin lispro during pregnancies and deliveries. One of these pregnancies was terminated at 20 weeks gestation and the second pregnancy resulted in a seemingly healthy infant after an elective cesarean delivery, but who subsequently died unexpectedly 3 weeks later. Both infants were discovered to have congenital abnormalities, which led the authors to question whether insulin lispro might have teratogenic effects on the fetus, in which case it should not be used during pregnancy. The report cites concerns about insulin lispro use during pregnancy, yet it does not provide conclusive evidence that insulin lispro was responsible for the malformations of the infants mentioned. In fact, there is sufficient reason to doubt that insulin lispro was to blame, since these isolated case reports were not part of a study and there was no control group. Therefore, the findings should stimulate initiation of clinical trials testing the safety of insulin lispro during pregnancy and not be taken as evidence that it is unsafe. Despite the opinion of Diamond and Kormas²⁸ that poor glycemic control was not responsible for the abnormalities of the infants in the cases described earlier, there is insufficient evidence to support this claim. The letter reports that A1C levels were determined every 3 months and that both women had values <7% at each test. However, an A1C of 7% may be associated with an increased risk of fetal malformations. Since organogenesis is complete within the first 7 weeks of pregnancy²⁹ and women tend to improve their glycemic control as the pregnancy progresses, an A1C measured at 3 months of pregnancy is a poor reflection of the mother's blood glucose levels at conception and during the critical first organogenic weeks of pregnancy. The report also indicated that both women maintained a mean blood glucose level of <108 mg/dL. A pregnant woman's target blood glucose should be <90 mg/dL fasting and <120 mg/dL postprandially.²⁹ If the women measured their fasting blood glucose only, the reported mean is obviously too high. If postprandial measurements were also taken into account, the mean is still too high, although less so. These women would be categorized as being at high risk for bearing infants with malformations. Throughout pregnancy, the second mother was being treated for hypertension, and if the

malformations were due to a medication, it is perhaps unfair to single out insulin lispro. In spite of the medication used, the malformations reported are more indicative of poor glycemic control: situs inversus, one of the abnormalities in the first infant, occurs almost exclusively in children of diabetic mothers.^{30,31} During the initial clinical trials testing insulin lispro, pregnant women were excluded. However, some participants became pregnant unexpectedly during the trials, and 19 infants were born by these mothers who were using insulin lispro. Of these births, 1 child had a right dysplastic kidney but the other 18 were healthy.³² Now there is a report that shows that insulin lispro is not teratogenic. Wyatt et al.²² report has shown that insulin lispro is not associated with increased malformations. This report clearly showed that the 27 malformations that occurred in this data set of 500 exposed pregnancies only occurred in women whose A1C levels were greater than 2 standard deviations (SD) above the mean of the normal. There were no malformations in the sample of women whose A1C levels were within two SD of the normal. Thus the null hypothesis has been proven: insulin lispro does not by itself cause malformations. Malformations are only associated with hyperglycemia in the first trimester. Mathiesen et al.²³ have now reported that insulin aspart is safe and efficacious in pregnancy with no increase in malformation rate.

Possible effects of rapid-acting insulin analogs on the mother

There are three situations in life in which rapid normalization of blood glucose levels increase the risk for deterioration of diabetic retinopathy: puberty, pregnancy, and rapid normalization of blood glucose levels. If two of these events occur in the same patient, the risk for retinopathy progression is potentiated.^{33,34} All three situations are associated with increased serum concentrations of growth-promoting factors.³³ It is hypothesized that when the blood glucose level is rapidly decreased, there is increased retinal extravasation of serum proteins. If there is a concomitant increase in the concentration of serum growth-promoting factors, a predisposed retina may deteriorate. Pregnancy *per se* is the most frequently reported situation in which rapid normalization of blood glucose is associated with deterioration of retinal status. Normal pregnancy is associated with high concentrations of many growth-promoting factors.^{35–40} Hill et al.³⁷ reported that a potent mitogen and angiogenic factor normally absent from the adult circulation become detectable by 14 weeks of gestation and is maximal at 22–32 weeks of gestation. A placental growth hormone variant had been found to increase throughout pregnancy, along with hCS and prolactin.³⁸

The production of maternal insulin-like growth factor (IGF)-I has also been shown to increase significantly above nonpregnant levels.³⁴ It is well known that diabetes mellitus is associated with perturbations of growth hormone IGF-I in cases of poor metabolic control.³⁷ Kitzmiller et al.⁴¹ have suggested that treatment with insulin lispro during pregnancies

complicated by diabetes may be associated with acceleration of diabetic retinopathy. If treatment with lispro insulin did play a role in the rapid deterioration of retinopathy in the case reports, it most likely was not mediated by IFG-I activity of lispro. Human insulin binds to the IFG-I receptor with an affinity of 0.1%–0.2% that of IFG-I. A comparison of insulin lispro and human insulin was made to determine the relative IFG-I receptor binding affinity in human placenta membranes, skeletal muscle, smooth muscle cells, and mammary epithelial cells. Insulin lispro had a slightly higher affinity for the human placenta membranes when compared with human insulin (1.3 times greater than human insulin). No other differences were observed in any other cell lines. Despite the suggested increased affinity, it should be noted that the absolute affinity for the IFG-I receptor is extremely low for both insulin lispro and human insulin. Concentrations >1000 times above the normal physiologic range are needed to reach 50% receptor binding. IFG-I is a much larger protein chain than insulin, and there is a 49% homology between human insulin and IFG-I. The reversal of the B28 and B29 amino acids in insulin lispro increases this homology to 51%, because of the analogous position in the IGF molecule. It has been shown that insulin lispro has the same affinity for the IFG-I receptor as does human insulin; also, the dissociation kinetics of insulin lispro on the insulin receptor are identical to those of insulin, indicating that insulin lispro should have no excess mitogenic effect via either the IFG-I or the insulin receptor.^{42,43} Patients in the Kitzmiller reports⁴¹ all had elevated levels of IFG-I due to poor control of their diabetes and due to pregnancy *per se*, independent of the possible IFG-I activity of lispro. However, anecdotal cases should never be used to infer a cause–effect relationship. In controlled clinical trials of >2000 patients with insulin lispro, no significant differences in retinopathy were observed, but there were no pregnant women in this trial.¹⁵ The factors that emerge as the independent risk factors for retinopathy progression include elevated A1C at baseline, duration of diabetes, significant proteinuria (>300 mg/24 hours), pregnancy, and rapid normalization of blood glucose (in <14 weeks). In fact, the strongest risk factor for retinopathy progression, independent of baseline retinal status, is baseline elevation of A1C associated with a rapid decline to normal. Of 14 patients who were treated with insulin lispro during pregnancy, described by Kitzmiller et al.,⁴¹ 11 had risk factors, including the evidence of baseline retinopathy, which have been associated with progression to proliferative retinopathy during pregnancy. Therefore, we can learn the fact that if there is no retinopathy during the first trimester of a pregnancy complicated by diabetes, progression to proliferative retinopathy needing laser therapy is rare; however, many of the cited references earlier emphasize that baseline elevation of glucose associated with rapid normalization can accelerate retinopathy. Phelps et al.⁴⁴ clearly showed that deterioration of retinopathy correlated significantly with the levels of plasma glucose at entry and with the magnitude of improvement in glycemia during the first 6–14 weeks after entry. Although the 13 patients with no retinopathy at baseline did not progress to proliferative

retinopathy, 1 did develop moderate hemorrhages, exudates, and intraretinal microaneurysms. Of their 20 patients with initial background retinopathy, 2 progressed to proliferative retinopathy. Laatikainen et al.⁴⁵ confirmed that the decrease in A1C levels was most rapid in the two patients with the worst progression. They concluded that a rapid near normalization of glycemic control during pregnancy could accelerate the progression of retinopathy in patients with poorly controlled diabetes. The DIEP study³⁴ reported that 10.3% of diabetic women who progressed, despite no retinopathy at baseline, had an initial A1C elevation of four SD above the mean of a normal population (risk progression 40%, odds ratio [OR] 2.4). Independent of retinal status, the DIEP study also reported that the duration of diabetes increased the risk of progression such that after 6 years of duration of diabetes, the OR was 3.0; by 11–15 years, it was 9.7; and >16 years it was 15.0, but hyperglycemia was a stronger risk factor. Additional evidence has been reported by the Diabetes Control and Complications Trial (DCCT).⁴⁶ In the conventional care group who became pregnant ($n = 135$), and thus had immediate intensification of glucose control, 47% worsened their retinal status, and the OR for progression by the second trimester was 2.6 compared to diabetic women in the conventional group who did not become pregnant. In order to compare the A1C levels reported by the DCCT⁴³ to other published reports, the approximate equivalent baseline A1C levels, using the DCCT normal range, is 7.1%, 9.8%, and 9.5%, respectively. In addition, the rate of fall of the A1C level in the three case reports was faster than the reported rate of fall associated with deterioration of retinal status.

There is one case report in the literature that clearly shows that the combination of pregnancy and rapid normalization of severe hyperglycemia is sufficient to “explode” a previously normal retina. Hagay et al.⁴⁷ reported a case of a woman with no previously documented hyperglycemia who presented at 8 weeks of gestation with an HbA1C level of 16%, and her ophthalmic examination was reported to be “completely normal.” She was treated with intensive insulin therapy and at 12 weeks her A1C level was 5.9%. By the second trimester, she had severe bilateral proliferative diabetic retinopathy needing photocoagulation. In a report by Omori et al.⁴⁸ studying Japanese pregnant diabetic women, the prevalence of retinopathy was 34.4% in their type 2 diabetic population. In addition, the prevalence of proliferative retinopathy was as high in the women with type 2 diabetes as in the pregnant women with type 1 diabetes, despite the shorter duration of documented diabetes in their patients with type 2 diabetes. The need for photocoagulation occurred in 50% of their pregnant diabetic patients with type 2 diabetes with greater than background retinopathy at the beginning of pregnancy. If insulin lispro did play a role in the progression of retinopathy, it is more likely that the insulin lispro facilitated the rapid normalization of the blood glucose levels. In pregnant diabetic patients, it has been shown that insulin lispro improves glucose control and thus significantly lowers the A1C level compared to patients who are administered by human regular insulin.^{17,22} There is danger in normalizing blood glucose quickly, regardless of the type of insulin used,

in pregnant women with a long duration of diabetes and elevated A1C levels in the first trimester, in those with proteinuria and perhaps those with type 1 diabetes. To date, there have not been extensive clinical trials on the retinal status of women treated with insulin aspart (or any other insulin analog) in pregnancy. Thus, we await clinical trials of the use of all of the insulin analogs in pregnancy to make a decision about the role of analogs in the progression of retinopathy during pregnancy. Busy clinics may have a decreased ability to examine retinæ thoroughly. Mild background retinopathy may be missed, even in the best of settings. Any retinopathy increases the risk, especially if the blood glucose level is elevated. Rather than recommending angiography to all women before each pregnancy is planned, in the case of no retinopathy seen on retinal examination, it is prudent to improve the glucose control slowly. These case reports reinforce the need to intensify preconceptional care programs to allow the luxury of slowly normalizing the blood glucose and to plan the pregnancy only after the blood glucose levels have been stabilized in the normal range for at least 6 months.^{46–48} If a patient presents pregnant, with high A1C levels, regardless of the retinal status, as suggested by these cases, then a retinal specialist needs to be on the team, be vigilant, and treats any developing angiopathy while the blood glucose is normalized. If an insulin analog was available that was not immunogenic and had the rapid action of insulin lispro but had less IFG-I activity than human insulin, then even if there was no proof that the IFG-I activity of the insulin plays a role in the acceleration of diabetic retinopathy when the blood glucose level is normalized quickly, such an insulin would become the treatment of choice. Insulin aspart, an insulin analog that has been shown to produce a peak blood level at 40 minutes and lowers the postprandial glucose levels significantly better than human insulin, has only 69% the IFG-I activity of human insulin.

Long-acting insulin analogs have only recently been used in clinical practice.⁴⁹ The first clinically available long-acting insulin analog is insulin glargine. Insulin glargine has a glycine substitution in the alpha chain at the 21 position and two glargines attached to the beta chain terminal at position 30. It is a soluble insulin and has been shown to provide peakless, sustained, and predictable 24 hours action. Of note, insulin glargine has a sixfold increase in IFG-I activity as compared to human insulin. There are no clinical trials using insulin glargine in pregnancy, nor are there reports of the retinal status in any of the 32 women in the previously published case reports of the use of glargine in pregnancy.^{24–27} However, a recent paper²⁷ describing 118 women treated with glargine during pregnancy showed that the macrosomia rate was increased fourfold over that reported using human insulins. Of note, insulin glargine has a sixfold increase in IFG-I activity as compared to human insulin. Another insulin analog that is currently in clinical trials is insulin detemir. Here again there are no trials using this insulin in pregnancy, but the studies show that detemir has the same IFG-I activity as human insulin.²⁷ Insulin detemir is now category B. The clinician has to keep in mind that the most important concern is to safely normalize the maternal

blood glucose. Before 1985, impure animal insulin was used, with a result that the IgG antibody levels rose the longer the women were treated. After 20 years of diabetes, women had antibody levels >10,000. Purified human insulin has been available for >20 years; thus there is a new generation of type 1 diabetes in women who have never been treated with animal insulins and therefore have negligible antibodies. Before giving these women insulin analogs, it must be proved that (1) they do not cause an immunologic response, (2) they do not cross the placenta, (3) they do not increase the risk of congenital anomalies or spontaneous abortions, and (4) they do not significantly increase the serum IFG-I levels or accelerate diabetic retinopathy.

Definition of normoglycemia based on infant outcome

Previously, glucose control and targets for treatment were based on clinical judgment and concern for hypoglycemia. In fact, most clinicians preferred to maintain hyperglycemia rather than increase the risk of a hypoglycemic reaction. As tools and techniques improved to achieve near-normal glucose levels during pregnancy, the emphasis has changed to strive for the degree of maternal metabolic control that is associated with normal body size and proportions in full-term infants. Mello et al.⁵⁰ published a study in which they investigated the anthropomorphic characteristics of 98 full-term singleton infants born to 98 women with type 1 diabetes. They reported that those women who had a mean daily blood glucose level <95 mg/dL had normal infants whereas the women with mean blood glucose levels >95 mg/dL delivered infants with an increased prevalence of being large for gestational age, with a significantly greater ponderal index and thoracic circumference with respect to the control group. Others have confirmed that overall mean glucose levels of <95 mg/dL can avoid alterations in fetal growth.⁵ Jovanovic et al.⁵¹ studied 52 women with type 1 diabetes and found that when the mean blood glucose was maintained between 80 and 84 mg/dL, the outcome of pregnancy was normal. Langer et al.⁵² assessed the relationship between optimal levels of glycemic control and perinatal outcome in a prospective study of 334 women with GDM and found that when the mean glucose levels were <86 mg/dL, this group had a significantly higher prevalence of SGA infants. In contrast, when the mean glucose levels were >105 mg/dL, there was a 20% prevalence of large-for-gestational-age infants. Hellmuth et al.⁵³ found that the frequency of hypoglycemia, especially nocturnal hypoglycemia, was seen with a prevalence of 37% in the first trimester of pregnancies treated with intensified insulin therapy. Sacks et al.⁵³ studied 48 women with type 1 diabetes and 113 women with type 2 diabetes during pregnancy. They found that the mean glucose levels were higher in the patients with type 1 diabetes and at least one daily glucose level was <50 mg/dL during 19% of observational days compared to only 2% of days in the type 2 diabetes group. Rosenn et al.⁵⁴ and Rosenn and Miodovnik⁵⁵

published papers on the topic of the increased risk of hypoglycemia during pregnancies complicated by diabetes. They found that at least 40% of mothers reported hypoglycemia during pregnancy. Clinically significant hypoglycemia requiring assistance from another person occurred in 71% of the 84 women studied, with a peak incidence occurring between 10 and 15 weeks of gestation. They did not observe any increase in embryopathy. Jovanovic et al.⁵⁶ then published the first-trimester insulin requirements of women studied in the DIEP study. They showed that there was a drop in insulin requirements during 8–11 weeks of gestation, which was seen in all women with type 1 diabetes whose glucose concentrations were insensitively managed. The majority of decreases in the insulin requirement were seen in the overnight period. It was concluded that the insulin doses needed to be decreased for the overnight insulin requirement to prevent nocturnal hypoglycemia during the late first trimester.

Insulin requirements

Women with type 1 diabetes must increase their insulin dosage to compensate for the diabetogenic forces of normal pregnancy. However, the exact pattern of insulin dosage increase is still controversial. Many observers have detected a decline in insulin requirement late in the first trimester of diabetic pregnancies. Jorgen Pedersen, the father of the study of diabetes in pregnancy, was among the first to observe that first-trimester hypoglycemia was a symptom of pregnancy and that it was a common knowledge among the physicians of today. Pedersen wrote:

Those physicians who manage diabetic women should be particularly alert for hypoglycemia in women who have recently become pregnant. About the 10th week of gestation there is an improvement in glucose tolerance manifesting itself as insulin coma, milder insulin reaction or an improvement in the degree of compensation. When a reduction in insulin dosage is called for it amounts to an average of 34%.

Indeed, he even claimed that “Once in a while pregnancy may be diagnosed on account of inexplicable hypoglycemic attacks.” In a total of 26 cases of insulin coma collected, all of the cases in his series occurred in months 1–4 of gestation, with the majority occurring at months 2–3. He also noted that by late gestation, regardless of the metabolic control and duration of diabetes, average daily insulin requirements increased by twofold from earlier in pregnancy. Early first-trimester overinsulinization might explain a later first-trimester drop in insulin requirement. One example of this effect may be the significantly greater weight gain seen in the first trimester by diabetic women compared to healthy nondiabetic women. Perhaps the drive to increase caloric intake to prevent hypoglycemia in the first trimester may have been the cause of the first-trimester excessive weight gain in the diabetic women compared to the controls. On the other hand, others have not seen the first-trimester

decrease in insulin requirement. There are also reports of rising insulin requirement in the first trimester. The present authors have described the insulin requirements during pregnancy of a population of women with well-controlled type 1 diabetes, which possibly lends credence to the notion that first-trimester overinsulinization may be the cause of the hypoglycemia seen by some workers in the first trimester. In addition, together with the DIEP study group, the present authors have analyzed the insulin requirement and stratified based on the degree of glucose control in the first trimester.⁵⁶ The weekly insulin requirement (as units/kg/day) were examined in the first trimester of diabetic women in the DIEP study with accurate gestational dating, regular glucose monitoring, daily insulin dose recording, and monthly A1C measurements. In pregnancies that resulted in live-born, term, singleton infants, a significant increase in mean weekly dosage was observed in weeks 3–7 ($p < 0.001$), followed by a significant decline in weeks 8–15 ($p < 0.001$). The Friedman nonparametric test localized significant changes to the interval between weeks 7–8 and weeks 11–12. To determine if prior poor glucose control exaggerated these trends, the women were divided based on their A1C values: <2 SD above the mean of a normal population (group 1), 2–4 SD (group 2), and >4 SD (group 3) at baseline. Late first-trimester declines in dosage were statistically significant in group 2 ($p = 0.002$) and in groups 2 and 3 together ($p = 0.003$). Similarly, women with body mass index >27.0 had a greater initial insulin rise and then a fall compared to leaner women. Observations in the DIEP study cohort disclosed a mid-first-trimester decline in insulin requirement in pregnant women with insulin-dependent diabetes. Possible explanations include overinsulinization of previously poorly controlled diabetes and a transient decline in progesterone during the late first-trimester luteoplacental shift in progesterone production. Clinicians should anticipate a reduction in insulin requirement in the 4-week interval between weeks 8 and 12 of gestation. Based on these studies of women with well-controlled diabetes, an algorithm for care and an insulin requirement protocol has been created based on gestational week and the woman’s current pregnant body weight. The total daily dose of insulin in the first-trimester (weeks 5–12) insulin requirement is 0.7 unit/kg/day; in the second trimester (weeks 12–26), the insulin requirement is 0.8 unit/kg/day; in the third trimester (weeks 26–36), the insulin requirement is 0.9 unit/kg/day; and at term (weeks 36–40), the insulin requirement is 1.0 unit/kg/day (Table 23.1). The insulin needs to be divided throughout the day to provide the basal need (the dose of insulin that keeps a woman normal in the fasting state) and meal-related need.

When multiple insulin injections are used to provide the basal need, NPH insulin is preferred because it has a more predictable absorption pattern than Lente or Ultralente insulin. Also, the recently developed long-acting insulin analog, insulin detemir, has just received the FDA category B determination. The preferred use of NPH is to give one-sixth of the total daily dose of insulin (I) as morning, dinner, and bedtime injections (i.e., NPH dose equals 50% of daily dose divided into three equal injections of NPH given every

Table 23.1 Insulin dosage regimen for diabetic pregnancy

Pregnancy NPH plus rapid-acting insulin schedule			Patient weight in kg =		Date and time:
"Big I" = total daily units of insulin					
Circle one: gestational weeks	13–28	29–34	35–40	Other	
= 0–12					
$k = 0.7$	0.8	0.9	1.0		
Calculate desired units of insulin from above line.					
"Big I" = $\frac{k \text{ units} \times \text{weight kg}}{24 \text{ hours}}$					
"Big I" = basal insulin requirement + bolus (meal related) insulin requirement					
Basal = $\frac{1}{2}$ "Big I," bolus = $\frac{1}{2}$ "Big I"					
Basal: Divide so that $\frac{1}{3}$ of "Big I" is NPH given before breakfast, $\frac{1}{3}$ of "Big I" is NPH given before dinner, and $\frac{1}{3}$ of "Big I" is NPH given before bedtime.					
Bolus: Divide so that $\frac{1}{3}$ of "Big I" is rapid-acting insulin given before breakfast, $\frac{1}{3}$ of "Big I" is rapid-acting insulin given before lunch, and $\frac{1}{3}$ of "Big I" is rapid-acting insulin given before dinner. The rapid-acting insulin is then titrated based on the blood glucose.					
0800 Prebreakfast: NPH = $\frac{1}{3}$ "Big I" = ____					
Check yesterday's predinner BS:					
If yesterday's predinner BS < 60, then decrease today's a.m. NPH by 2 units.					
If yesterday's predinner BS 61–90, no change in today's a.m. NPH.					
If yesterday's predinner BS > 91, then increase today's a.m. NPH by 2 units.					
Do not feed the patient until the blood sugar is below 120 mg/dL.	Rapid-acting insulin = "Big I" = : to be adjusted according to the following scale:				
	Prebreakfast BS < 60 = ____ = $(\frac{1}{3} \text{ "Big I" dose}) - 3\% \text{ of the "Big I."}$				
	61–90 = ____ = $\frac{1}{3} \text{ "Big I" dose.}$				
	91–120 = ____ = $(\frac{1}{3} \text{ "Big I" dose}) + 3\% \text{ of the "Big I."}$				
	>121 = ____ = $(\frac{1}{3} \text{ "Big I" dose}) + 6\% \text{ of the "Big I."}$				
	If today's BS 1 hour after breakfast is <110, then decrease tomorrow's prebreakfast rapid-acting insulin by 2 units.				
	If today's BS 1 hour after breakfast is 111–120, no change in tomorrow's prebreakfast rapid-acting insulin.				
	If today's BS 1 hour after breakfast is >121, then increase tomorrow's prebreakfast rapid-acting insulin by 2 units.				
	1200 Prelunch: Rapid-acting insulin is Vs "Big I" = ____ to be adjusted according to the following scale:				
	Prelunch BS < 60 = ____ = $(\frac{1}{3} \text{ "Big I" dose}) - 3\% \text{ of "Big I."}$				
Do not feed the patient until the blood sugar is below 120 mg/dL.	61–90 = ____ = $\frac{1}{3} \text{ "Big I" dose.}$				
	91–120 = ____ = $(\frac{1}{3} \text{ "Big I" dose}) + 3\% \text{ of "Big I."}$				
	>121 = ____ = $(\frac{1}{3} \text{ "Big I" dose}) + 6\% \text{ of "Big I."}$				
	If today's BS 1 hour after lunch is <110, then decrease tomorrow's prebreakfast rapid-acting insulin by 2 units.				
	If today's BS 1 hour after lunch is 111–120, no change in tomorrow's prebreakfast rapid-acting insulin.				
	If today's BS 1 hour after lunch is >121, then increase tomorrow's prebreakfast rapid-acting insulin by 2 units.				

(Continued)

Table 23.1 (Continued) Insulin dosage regimen for diabetic pregnancy

1700 Predinner: NPH = "Big I" = ____ Do not feed the patient until the blood sugar is below 120 mg/dL.	Rapid-acting insulin is $\frac{1}{2}$ "Big I" =: to be adjusted according to the following scale: If yesterday's prebedtime BS < 60, then decrease today's dinner NPH by 2 units. If yesterday's prebedtime BS 61–90, no change in today's dinner NPH. If yesterday's prebedtime BS > 91, then increase today's dinner NPH by 2 units. Predinner BS < 60 = ____ = ($\frac{1}{2}$ "Big I" dose) – 3% of "Big I." 61–90 = ____ = $\frac{1}{2}$ "Big I" dose. 91–120 = ____ = ($\frac{1}{2}$ "Big I" dose) + 3% of "Big I." >121 = ____ = ($\frac{1}{2}$ "Big I" dose) + 6% of "Big I." If today's BS 1 hour after dinner is <110, then decrease tomorrow's dinner rapid-acting insulin by 2 units. If today's BS 1 hour after dinner is 111–120, no change in tomorrow's dinner rapid-acting insulin. If today's BS 1 hour after dinner is >121, then increase tomorrow's dinner rapid-acting insulin by 2 units.
2400 Bedtime NPH: Give $\frac{1}{2}$ "Big I" = ____	If today's prebreakfast BS is <60, then decrease today's bedtime NPH by 2 units. If today's prebreakfast BS is 61–90, no change in today's bedtime NPH. If today's prebreakfast BS is >91, then check the 3 a.m. BS, and, if it is <70 (regardless of today's prebreakfast BS), decrease today's bedtime NPH by 2 units. If today's prebreakfast BS is >91 and the 3 a.m. BS > 70, increase today's bedtime NPH by 2 units. Also, if the 3 a.m. BS is > 91, then call the doctor for 3 a.m. rapid-acting insulin scale equal to the prelunch rapid-acting insulin scale.

8 hours, or at 8 a.m., 4 p.m., and 12 midnight; Table 23.1). The other half of the total daily insulin dose should be a rapid-acting insulin (insulin lispro or insulin aspart) given before each meal to control postprandial glycemia (Table 23.1). This dose of rapid-acting insulin can be given using the insulin infusion pump or by multiple doses of subcutaneously injected insulin (Tables 23.1 through 23.3). The meal-related insulin dose (one-half of the total daily insulin requirement [0.5I]) (Table 23.1). The exact division of this meal-related insulin dose depends on the size of the woman's lunch versus her dinner. Compensatory doses to adjust for high or low glucose levels are calculated as 3% of

the total daily insulin requirement. Clinicians should note that hyperglycemia would occur if the patient used only insulin lispro or insulin aspart for the meal-related needs and if the woman goes a long time between meals. The dose of NPH insulin may not be sufficient to prevent an escape of the blood glucose before the next dose of insulin is given. To prevent this escape of blood glucose when >3 hours elapse between injections of the rapid-acting insulin analogs of lispro or aspart, the patient should add 3% of her total daily insulin requirement as regular human insulin to the lispro injection to extend the effectiveness of the rapid-acting component.

Table 23.2 Basal insulin pump program (using human regular, insulin lispro, or insulin aspart)

Period	Basal requirement (B ^a) (hourly infusion rate)	Rationale
Midnight to 4 a.m.	50% less basal (B/24 × 0.5)	Maternal cortisol at nadir
4–10 a.m.	50% more basal (B/24 × 1.5)	Highest level of maternal cortisol
10 a.m. to noon	Basal (B/24)	
<i>Note:</i> To refine basal settings, have the patient perform self-monitoring blood glucose at the end of each period to determine whether adjustments are needed. For instance, at the 4 a.m. test, the blood glucose level should be 60–90 mg/dL; if blood glucose level is out of this range, dial up or down insulin in increments of 0.10 unit/hour. (Consider using 0.1 unit/kg as NPH insulin at bedtime to prevent diabetic ketoacidosis secondary to needle slippage; then decrease the overnight basal from 4 to 10 a.m. by 0.02 unit/kg/hour.)		
^a B = 0.5I (the total daily insulin) or an hourly rate of B/24.		

Table 23.3 Premeal sliding scale dose calculation using rapid-acting insulin^a

Premeal basal glucose (mg/dL)	Compensatory insulin
<60	Meal-related insulin dose minus 3% ^{1b}
61–90	Meal-related insulin dose: no adjustment necessary
91–120	Meal-related insulin dose plus 3% ^{1b}
121	Meal-related insulin dose plus 6% ^{1b}

^a Human regular insulin or insulin lispro or insulin aspart.

Insulin infusion pumps

Insulin infusion pumps have been used for treatment for over two decades.⁵⁷ However, the data on the safety and efficacy of insulin pumps during pregnancies complicated by diabetes are still in its infancy. Kitzmiller et al.⁵⁸ showed that insulin pump therapy did improve glucose control and minimized clinically significant hypoglycemic events to 2.2/week. Coustan et al.⁵⁹ then reported a randomized clinical trial of insulin pump therapy versus conventional therapy in pregnancies complicated by diabetes. They showed that there were no differences between the two treatment groups with respect to outpatients' mean glucose levels, symptomatic hypoglycemia, or HbA1C levels. They concluded that excellent diabetes control can be achieved with both insulin infusion pumps and with multiple injections of insulin. Carta et al.⁶⁰ also performed a randomized trial of continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in pregnant women with type 1 and type 2 diabetes. They reported that there were not significant differences in mean insulin requirements at the different stages of gestation and that perinatal outcome was satisfactory in both groups; however, in their study, control of fetal growth was better with interfiled convention therapy compared to fetal growth in the pump group. Mancuso et al.⁶¹ studied the efficacy of the insulin pump in the home treatment of pregnant diabetic women. They reported that seven women with type 1 diabetes, who used the pump, delivered term infants and had no macrosomia or neonatal problems along with normal glucose tolerance tests at 2 years of life.

Potter et al.⁵⁷ studied continuous insulin infusion in the third trimester of eight pregnancies complicated by diabetes.

Compared to historical controls, they concluded that diurnal variations of blood glucose concentrations were dampened. Leveno et al.⁶² performed a case-controlled trial of insulin pump therapy versus intensified conventional therapy and observed no significant differences between the groups for glucose control, cost, and complications. They concluded that insulin pumps were not acceptable to all pregnant diabetic women and that such therapy may

not be necessary to improve pregnancy outcome. Caruso et al.⁶³ treated 12 women with poorly controlled pregnant diabetes with insulin infusion pumps and showed that glucose levels could be quickly normalized with a remarkable decrease in variation of glucose excursions. In addition, they showed that insulin, glucose, and C-peptide levels in the amniotic fluid were normal and none of the infants were macrosomic or had any neonatal problems. They concluded that insulin infusion pump therapy was highly effective compared to intensified conventional treatment. In a nested case-controlled study, Simmons et al.⁶⁴ utilized insulin pumps in pregnancies complicated by type 2 diabetes and GDM in a multiethnic community and showed in 30 women that none experienced severe hypoglycemia and 79% had improved glycemic control within 1–4 weeks. Mothers using the pump had greater insulin requirements and greater weight gain. Although their infants were more likely to be admitted to the special care unit, they were not heavier nor did they have more hypoglycemic events than control subjects. Jensen et al.⁶⁵ reported their series using insulin infusion pump therapy ($n = 11$) in the preconception treatment period in women with type 1 diabetes compared to women treated with conventional therapy ($n = 9$). Two fetuses born of mothers treated with conventional therapy exhibited early group delay, whereas all 11 fetuses born of mothers treated with pump therapy were normal; there were no malformations in either group. Gabbe et al.⁶⁶ published a series of 24 patients with type 1 diabetes and reported no difference, in the groups of women treated with pump compared with those treated with intensified insulin therapy for episodes of hypoglycemia, in the costs, complication, glycemic control, or pregnancy outcome. The advantages seen were all postpartum because those women who were on the pump into their postpartum period sustained better glucose control than those who were on intensified insulin therapy during pregnancy.

The conclusion drawn from this review of the literature on using insulin pump therapy in pregnant women with diabetes is that pump therapy is not necessary in order to achieve and maintain optimal control (27.4); however, 5 of the 10 papers suggest that insulin pump therapy has an advantage over intensified multiple injections of insulin. In addition, only 155 patients were reported in these 10 trials, and in all but one paper, the women had their pump therapy started in the second or third trimester (Table 23.4).

Insulin algorithms for continuous insulin infusion pump therapy in pregnancy

The basal need is usually 50% of the total daily insulin dose (0.5I) and may be delivered using a constant infusion pump (Table 23.2) or by multiple doses of intermediate-acting insulin (Table 23.1). When using a constant infusion pump,

Table 23.4 Review of the literature on using insulin infusion pump therapy in pregnancies complicated by diabetes

Author (reference)	No. on CSII ^a	Trimester or weeks of gestation	Type of DM ^b	Type of trial/comments
Potter et al. ⁵⁷	8	Third	1	Longitudinal/improved
Kitzmiller et al. ⁵⁸	24	5–10	1	Longitudinal/no difference
Coustan et al. ⁵⁹	22	Second and third	1	Randomized/no difference
Carta et al. ⁶⁰	14	First	1	Case control/improved
Mancuso et al. ⁶¹	12	Third	1	Longitudinal/improved
Jensen et al. ⁶⁵	9	Before and all trimesters	1	Case control
Caruso et al. ⁶³	12	Third	1	Longitudinal/improved
Leveno et al. ⁶²	11	Second and third	1	Self-selection/no difference
Gabbe et al. ⁶⁶	23	Second, third, and postpartum	1	Only postpartum improved
Simmons et al. ⁶⁴	30	Second	GDM and 2 ^c	Equal

^a Continuous subcutaneous insulin infusion.
^b Diabetes mellitus.
^c Gestational diabetes mellitus.

the basal need is calculated as an hourly rate (Table 23.2) and is delivered such that the calculated rate (0.5I or total dose over 24 hours divided by 24) is given between 10 a.m. and midnight. The rate is cut in half (i.e., 0.5I divided by 24 times 0.5) from midnight to 4 a.m. and increased by another 50% (i.e., 0.5I divided by 24 times 1.5) to counteract the morning rise of cortisol levels that are potentiated during pregnancy. Also, low-dose NPH before bedtime has been used by some clinicians to prevent the possible occurrence of diabetic ketoacidosis if the needle slips out of position during the overnight period. This dose of NPH insulin needs to be sufficient to provide protection from ketosis, or 0.1 unit of NPH times the weight of the women in kilograms. Then the overnight basal insulin needs to be decreased to allow for the NPH dose. The 4–10 a.m. basal insulin should thus be adjusted downward by 0.02 unit/kg/hour.

Insulin and glucose treatment during labor

With improvement in antenatal care, intrapartum events play an increasingly crucial role in the outcome of pregnancy. The artificial beta cell may be used to maintain normoglycemia during labor and delivery, but normoglycemia can be maintained easily by subcutaneous injections. Before active labor, insulin is required, and glucose infusion is not necessary to maintain a blood glucose level of 70–90 mg/dL. With the onset of active labor, insulin requirements decrease to zero, and glucose requirements are relatively constant at 2.5 mg/kg/minute. From these data, a protocol for supplying the glucose needs of labor has been developed.⁶⁷ The goal is to maintain the maternal plasma glucose between 70 and 90 mg/dL. In cases of the onset of active spontaneous labor, insulin is withheld and an intravenous (i.v.)

dextrose infusion is begun at a rate of 2.55 mg/kg/minute. If labor is latent, normal saline is usually sufficient to maintain normoglycemia until active labor begins, at which time dextrose is infused at 2.55 mg/kg/minute. Blood glucose is then monitored hourly, and if it is <60 mg/dL, then the infusion rate is doubled for the subsequent hour. If the blood glucose rises to >120 mg/dL, 2–4 units of regular insulin are given i.v. each hour until the blood glucose level is 70–90 mg/dL. In the case of an elective cesarean section, the bedtime dose of NPH insulin is repeated at 8 a.m. on the day of surgery and every 8 hours if the surgery is delayed. A dextrose infusion may be started if the plasma glucose level falls to <60 mg/dL, and 2–4 units of regular insulin given i.v. every hour if the blood glucose rises to >120 mg/dL.⁶⁷

Insulin and glucose requirements postpartum

Maternal insulin requirements usually drop precipitously postpartum, possibly for 48–96 hours. Insulin requirements should be recalculated at 0.6 unit/kg based on the postpartum weight and should be started when the 1-hour postprandial plasma glucose value is >150 mg/dL or the fasting glucose level is >100 mg/dL. The postpartum caloric requirements are 25 kcal/kg/day, based on the postpartum weight. For women who wish to breastfeed, the calculation is 27 kcal/kg/day and insulin requirements are 0.6 unit/kg/day. The insulin requirement during the night drops dramatically during lactation, owing to the glucose siphoning into the breast milk. Thus, the majority of the insulin requirement is needed during the daytime to cover the increased caloric needs of breastfeeding. Normoglycemia should especially be prescribed for nursing diabetic women, because hyperglycemia elevates milk glucose levels.⁶⁸

Conclusions

With the advent of tools and techniques to maintain normoglycemia before, during, and between all pregnancies complicated by diabetes, infants of diabetic mothers now have the same chances of good health as those infants born to the nondiabetic woman. Animal and human studies clearly implicate glucose as the teratogen. These studies, and

others, emphasize the need for preconception programs and the need for support systems to facilitate the maintenance of normoglycemia throughout pregnancy. The morbidity and subsequent development of the infant of the diabetic mother is associated with hyperglycemia. Therefore, the goal of insulin therapy is to achieve and maintain normoglycemia before, during, and after all pregnancies complicated by diabetes.

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24 Use of oral hypoglycemic agents in pregnancy

Oded Langer

Introduction

Gestational diabetes mellitus (GDM) continues to be a major public health problem for the mother and unborn fetus with an estimated incidence of 3%–10% depending upon geographic location; it affects at least 105,000–350,000 women annually in the United States. The cornerstone of treatment is a diabetic diet, and when dietary modifications do not control maternal glycemia, pharmacological therapy is initiated. The administration of short- and long-acting insulin is required in 20%–60% of pregnancies that are complicated by GDM in order to maintain adequate glycemic control. Based on its high efficacy, 50%–80% of patients will achieve the targeted level of glycemic control.¹ Insulin is inconvenient and expensive, which makes it an even greater concern in developing countries. Therefore, there has been an unrelenting search for a safe and effective alternative to insulin therapy especially in GDM and type 2 diabetes.

The prevalence of type 2 diabetes and GDM has increased by 33% in the past decade in the United States.² This may be attributed to the increased rate of obesity in the general population in all ethnic groups and the trend toward advanced maternal age in pregnancy. Because of the relative ease of administration and the low cost involved in overall therapy with oral hypoglycemic agents, they have become the drug of choice in the treatment of type 2 diabetes. One can assume that their popularity will only increase in the future, especially after confirmation from the large prospective study by the United Kingdom Prospective Diabetes Study (UKPDS) group. The results demonstrated that patients with type 2 diabetes can maintain the targeted level of glycemic control, thereby lowering the risk for microvascular complications.³ The use of oral hypoglycemic agents in nonpregnant patients with type 2 diabetes has become the standard of care in the United States.^{3,4} The randomized study of the use of oral hypoglycemic agents demonstrated that glyburide is an efficacious alternative to insulin in the treatment of diabetes in the pregnant subject.⁵

The prevalence of GDM varies in direct proportion to the prevalence of type 2 diabetes in a given population or ethnic group. In the United States, the prevalence rate ranges

from 1% to 19%. Among different ethnic groups, type 2 diabetes and GDM have been diagnosed in varying rates.^{6,7} Both are heterogeneous disorders whose pathophysiology is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining beta-cell function. It has become the prime objective for the treatment of both pregnant and nonpregnant diabetic patients to optimize the glycemic profile.^{8–10}

The controversy and historic ban on the use of oral hypoglycemic agents in pregnancy has been based on scant evidence from case reports^{11,12} and one study in particular on fetal anomalies in 50 patients with poorly controlled diabetes prior to pregnancy¹³ begs the question: is it the drug or is it the glucose? In the past decade, the use of oral hypoglycemic agents in pregnancy have become widely used in the United States following the recommendation of the American College of Obstetrics and Gynecologists (ACOG),¹⁴ evidence-based analysis of the data,¹⁵ and editorials and clinical opinions.^{16–20} Despite the fact that oral hypoglycemic agents (first-generation sulfonylureas) have been historically prescribed, both in the United Kingdom and South Africa, presently the use of glyburide (glipizide and metformin) is less widespread in Europe even though there is no reported adverse side effects to the fetus.^{21–26}

The purpose of this review is to provide the evidence and the foundation for understanding the use of oral hypoglycemic drugs in pregnancy as an effective alternative to insulin therapy in achieving glycemic control. The concerns of teratogenicity due to possible placental transfer, neonatal and maternal outcome, and basic pharmacological benefits will be addressed.

Oral hypoglycemic agents: Classification and characteristics

The oral hypoglycemic agents act, depending upon the specific group, directly upon the beta cells to increase insulin secretion and/or to decrease hepatic glucose production and increase peripheral insulin sensitivity. The advantage of using these agents rather than administering exogenous insulin is their ability to have an impact by nutrient availability and

extrapancreatic effect and/or to increase insulin availability through the physiological route.

The reader should consider the following “drug compass” when contemplating the use of oral hypoglycemic agents in pregnancy:

1. Will the drug–drug interactions complicate its use with the necessary and commonly administered drugs?
2. Can glycemic control be achieved by using the optimal dose?
3. After nutrient ingestion, can the drug reduce the time lag between the plasma glucose rise and insulin secretion?
4. Can serious postprandial and fasting hypoglycemia be minimized because the drug duration of action is short enough or its dependence on plasma glucose levels sufficient?
5. Are there any side effects that can reduce long-term beneficial effects?

A major consideration in the efficacy of the drug will be its ability to cross the placenta and, if so, what toxicity, if at all, can it cause to the developing fetus. Often, the fear of drug-induced adverse outcome, especially after the thalidomide era of the 1960s, inhibits the physician’s ability to judge the scientific rationale for using a drug and evaluating it using evidence-based data instead of dogma. Very few medications have been shown not to cross the placental barrier. In fact, a pregnant woman is often exposed to four or five prescription drugs during pregnancy for a variety of complaints. Similar to other epithelial barriers, transfer of drugs across the placenta is affected by several factors: molecular weight, pK_a , lipophilicity, placental blood flow, blood protein binding, elimination half-life, and the specific placental transport system that affects the ability of drugs to enter the fetal compartment.^{27–29}

Sulfonylureas

Sulfonylureas were discovered accidentally. Additional clinical trials led to the discovery of tolbutamide in the 1950s, and since that time, many drugs in this class have been developed, e.g., chlorpropamide. Second-generation sulfonylureas were subsequently developed that today include glyburide and glipizide. In 1997, the first drug in a new class of oral insulin secretagogues called meglitinides (benzoic acid derivatives) was approved for clinical use. The agent, repaglinide, has gained acceptance as a fast-acting, premeal therapy to limit postprandial hyperglycemia.²⁷ Sulfonylureas have been used in the treatment of type 2 diabetes since 1942 because of their capacity to cause hypoglycemia by stimulating insulin release from pancreatic beta cells. Sulfonylureas bind to specific receptors on beta cells that force the closure of potassium adenosine triphosphate channels and open calcium channels that cause an increase in cytoplasmic calcium stimulating insulin release. The major effect of these drugs is to enhance insulin secretion.^{30–34} Sulfonylureas may also further increase insulin levels by reducing hepatic clearance of the hormone, the main contributor to fasting

hyperglycemia. Enhanced insulin secretion diminishes glucose toxicity and improves insulin secretion after meals, thus reducing postprandial hyperglycemia. The drugs can also enhance peripheral tissue sensitivity to insulin.^{30,31} Sulfonylureas influence insulin secretion in direct proportion to plasma glucose levels from 60 to 180 mg/dL: they do not stimulate insulin secretion when the plasma glucose is <60 mg/dL.^{35,36} The mechanism of action of sulfonylureas is to facilitate rapid insulin secretion in response to nutritional intake, which results in minimal to no lag time between the changes in plasma glucose and modification of the insulin secretory rate.^{37,38}

Chlorpropamide has been available for more than 40 years and is a highly effective oral hypoglycemic agent with a very long duration of action. The main side effect for nonpregnant patients with type 2 diabetes is a significantly high rate of severe and protracted hypoglycemia. The complication has not been reported to be a major concern for pregnant patients in previous studies.^{21–25} The drug stimulates antidiuretic hormone secretion, potentiating its effect at the renal tubular level resulting in water retention and hyponatremia. With the development of second-generation sulfonylurea drugs that minimally cross the placenta, i.e., glyburide, first-generation drugs should not be recommended in pregnancy.²⁷

Glyburide (also known as glibenclamide and glybenzylamide) is one of the second-generation hypoglycemic sulfonylureas; the group also includes glipizide, gliclazide, and glimepiride. These are considerably more potent than the earlier agents. When given as a single agent, the peak plasma level of glyburide occurs within 4 hours; the absorption of the drug is not affected by food digestion. Metabolism of glyburide occurs in the liver and its metabolites are extracted in the bile and urine in equal proportions. Ten hours is the approximate elimination half-life of glyburide. Adverse effects of the drug are infrequent; they occur in less than 4% of patients receiving second-generation agents.²⁷ In 11%–38% of nonpregnant patients with type 2 diabetes, the main side effect of glyburide is hypoglycemia, with symptoms being dose related: the older patient is at greater risk of a hypoglycemic episode.

The patient most receptive to glyburide therapy is one who has been hyperglycemic for less than 5 years, is willing to follow a dietary protocol, and is of either normal weight or obese. Characteristic features of both type 2 diabetes and GDM are beta-cell exhaustion and insulin resistance. Most often, patients of both diabetic types are comparable in obesity, are asymptomatic in the early stages of the disease, and have similar prevalence in the same ethnic group. Given the similarity of the phenotypic features of these complications, it is safe to assume that the use of glyburide may be beneficial in the prevention of maternal–fetal GDM complications.

Glimepiride is another sulfonylurea drug. Both this drug and glyburide displace one another from their respective binding sites. Glimepiride has a 2.5–3-fold faster rate of association and an 8–9-fold faster rate of dissociation from the beta-cell sulfonylurea receptor (SUR) binding site

than glyburide. This results in a more rapid release of insulin and a shorter duration of insulin secretion. Glimepiride significantly increases second-phase insulin secretion, whole-body glucose uptake, and insulin sensitivity.^{4,39,40} The increase in insulin sensitivity may be explained by studies demonstrating lower fasting plasma insulin and C-peptide levels in patients using the drug compared to glyburide-treated patients with comparable levels of glycemic control. It should be noted that, to date, glimepiride has not been tested for use in pregnancy.^{4,39,40}

Biguanides

Biguanides were recognized as early as 1920 but received clinical recognition in the United States only in the recent past. Phenformin, the primary drug in this group, was withdrawn from American and European markets because of the side effects of lactic acidosis. Its replacement, metformin, although used extensively in Europe, has only been recognized for use in the United States since 1995.²⁷ Metformin is an oral antihyperglycemic agent that is chemically and pharmacologically unrelated to the sulfonylureas. Metformin is a second-generation biguanide that was reintroduced and distributed in the United States after biguanide phenformin was withdrawn from the market in the 1970s; both were introduced in 1957. Metformin has universally been shown to be effective in improving the glycemic profile in diabetic patients. Its mechanism of action is thought to include decreased hepatic glucose production and intestinal absorption of glucose and increased peripheral uptake of glucose and utilization. The two latter mechanisms result in improved insulin sensitivity, i.e., decreased insulin requirements.^{41–43} Importantly, metformin does not stimulate insulin secretion and, therefore, does not cause hypoglycemia either in diabetic or in control patients. The drug acts by causing the translocation of glucose transporters from the microsomal fraction to the plasma membrane of hepatic and muscle cells.⁴³

Metformin has no significant effect on the secretion of glucagons, cortisol, growth hormone, or somatostatin. The mechanism by which metformin reduces hepatic glucose production is controversial, but the preponderance of data indicates an effect on the reduction of gluconeogenesis.⁴³ It has a strong safety and efficacy record, with a frequency of lactic acidosis one-tenth that of the parent drug. The incidence of lactic acidosis with metformin is 0.03 cases/1000 patients annually. The elimination of plasma half-life time is 6 hours. Therefore, patients with renal compromise should not receive metformin, since the risk of lactic acidosis increases with the degree of renal impairment and patient age. Metformin should be introduced gradually in 500 or 850 mg increments to a maximum of 2000 mg daily.^{41,42}

The peak plasma level when the drug is given as a single agent occurs within 4 hours. The extent of absorption is reduced with food intake, although it should be administered with meals to minimize gastrointestinal intolerance. Metformin is not metabolized and is eliminated unchanged in the urine. It has been effective in reducing plasma

triglyceride and cholesterol levels as well as in promoting weight loss in obese diabetic patients. Hypoglycemia is not an overt side effect of its use. Metformin does not stimulate the fetal pancreas to oversecrete insulin.⁴⁴ However, metformin in pregnancy crosses the placenta. Its concentration in the fetal compartment results in umbilical vein levels twofolds higher than the maternal serum. Its effects on the fetus are unknown.

Thiazolidinediones

Thiazolidinediones were introduced in 1997. The first agent, troglitazone, was reported to have a high rate of hepatic toxicity and as a result was withdrawn from the market. Newer agents in this class such as rosiglitazone and pioglitazone are widely used in clinical practice without reported hepatic toxicity. Thiazolidinediones are a class of drugs that may provide still another pharmacological alternative to insulin therapy, although to date there are no reported data on its use in pregnancy. Troglitazone, the first of these agents to be introduced, has been withdrawn from use because it was associated with severe hepatic toxicity, followed by a number of deaths. These oral hypoglycemic agents exert their principal effects by lowering insulin resistance in peripheral tissue. A decrease in systemic and local tissue lipid availability may also contribute to its positive effects in controlling diabetes.

Rosiglitazone and pioglitazone, other oral agents in this group, are more potent than troglitazone and claim to offer lower risk of hepatotoxicity. They are absorbed within 2 hours but the maximum clinical effect is not observed for 6–12 weeks. Liver function should be measured before the start of therapy and monitored once initiated. Studies also report considerable weight gain with the drugs.^{45,46} Similarities exist between rosiglitazone and glyburide in pharmacological characteristics that may suggest that there is a possibility that they minimally cross the placenta. If this proves to be the case, rosiglitazone and pioglitazone, just as glyburide and metformin, may be ideal agents for the management of GDM and type 2 diabetes in pregnancy, as a single therapy or in combination with glyburide.

Alpha-glucosidase inhibitors: Alpha-glucosidase inhibitors, which reduce intestinal absorption of starch and glucose (acarbose), have now been introduced into clinical practice.²⁷ Alpha-glucosidase inhibitors act by slowing the absorption of carbohydrates from the intestine, thereby reducing the postprandial rise in blood glucose. The postprandial rise is blunted in both normal and diabetic patients. Gastrointestinal side effects require gradual dosage increments over time after initiation of therapy. This group of drugs may be considered a monotherapy in elderly patients but are typically used in combination with other oral antidiabetic agents and/or insulin. Acarbose is the oral agent in this group currently in use; however, in pregnancy, it is less effective than glyburide in achieving targeted levels of glycemia. Therefore, its optimal use is as a secondary and not a primary drug of choice.^{47,48}

Rationale for the use of oral hypoglycemic agents in the management of gestational diabetes mellitus

The intensified insulin approach in the management of GDM has been shown to result in perinatal outcomes comparable to those in the general population; thus, it has become the method of choice for the control of glycemia.¹ A less invasive, efficacious alternative that achieves similar perinatal outcome while enhancing patient compliance has been a major diabetes research goal. The underlying principle for the use of oral hypoglycemic agents in pregnancy has been motivated by three factors, first of which is the similarity between type 2 diabetes and GDM. In addition to the insulin secretion and resistance abnormalities found in both conditions, there is a loss of the first-phase insulin secretion with a striking lag time between the postprandial rise in glucose and the presence of significant insulin at the peripheral sites.^{36,37} The result is in an early increase in postprandial glucose values. As discussed before, second-generation sulfonylurea agents are rapid in onset and have a short duration of action that makes them ideal agents for treatment in GDM and possibly in the very early stages of type 2 diabetes in pregnancy.

Second, GDM and patients with impaired glucose tolerance (IGT) are characterized by mild hyperglycemia in comparison to type 2 diabetics. However, this mild hyperglycemia is significantly elevated in comparison to nondiabetic women. As the disease progresses to type 2 diabetes, there is progressive loss of beta-cell function.^{49,50} In the presence of insulin resistance with obesity, pregnancy, and, especially, GDM, insulin secretion will initially increase to compensate for the impairment in insulin action. The ensuing decrease in secretion over time (50%–80%) will, in turn, result in the progression from normal glucose tolerance to GDM, from there to IGT and to type 2 diabetes.⁵⁰ Oral hypoglycemic agents have been successfully used to decrease glycemic levels in type 2 diabetic patients. Since GDM subjects have the mildest form of the glucose tolerance abnormality, it is reasonable to assume that the use of oral hypoglycemic agents in the treatment of GDM should be even more effective than its current use with type 2 diabetic patients.

Third, the UKPDS on type 2 diabetes supported the efficacy of the drugs and in particular the use of glyburide.³ The study demonstrated that with the use of glyburide, 70% of patients achieved a targeted level of glucose control with the most favorable effect achieved within the first 5 years of therapy.³ The study also reported a decrease in microvascular and macrovascular complications. Rather than crediting a specific therapy as the factor responsible for the reduced risk of complications, the authors concluded that improvement in glycemic control was the crucial factor in treating the disease.

The results of the UKPDS^{3,49,50} and the Diabetes Control and Complications Trial⁵¹ suggested that intensive therapy in patients with types 1 and 2 diabetes will result in

improved glycemic control and decrease in the complication rates. Thus, intensified therapy can, alone, provide the primary prevention for diabetic complications. Studies of pregnant diabetic women, including a study of >2000 women with GDM,¹ demonstrated that intensified therapy results in improvement in glycemic control and in perinatal outcomes similar to those in the nondiabetic population.

Congenital malformations: Is it the glucose or is it the oral hypoglycemic agent?

The incidence of congenital anomalies in nondiabetic women is 2%–3%; the rate increases to 7%–9% overall in pregnant diabetic patients and is even higher in poorly controlled diabetics and as the severity of the disease increases. An unanswered question remains: what is the toxic agent that triggers the development of malformations—is it the glucose or is it the oral hypoglycemic agent? This dilemma has led to several investigations of animal species or tissue cultures as a source for answers. These types of studies provide the conditions with which to test separately and together the effect of different drug doses in conjunction with varying levels of glucose. However, we are well aware that the findings of studies using laboratory mice do not automatically translate into use on humans.

Smithberg and Runner⁵² studied different hypoglycemia-inducing treatments, including insulin, tolbutamide, and fasting of prepuberal mice, as well as combination treatments involving nicotinamide plus insulin or tolbutamide. They were all found to be potent teratogens in one or more inbred strains of mice. Teratogenic treatments, with the exception of fasting, also cause a variable proportion of deaths. The response of different strains of mice to individual treatments relevant to teratogenicity or lethality was highly variable. It is the variability of response elicited from each strain of mouse as a group that may be the most pertinent finding in these experiments. Most noteworthy is the 3% mortality produced by insulin treatment in strain BALB/c as compared to 17% in other strains. This example demonstrates the variability in study results reported in the literature. It also makes one realize that it was the strain of mouse that was the determining factor in recommending or failing to recommend a particular drug.

First-generation sulfonylureas, such as tolbutamide and chlorpropamide, were found to be associated with congenital malformations in the majority of animal studies. Adverse effects appear to be caused by the drugs and not by the hypoglycemia they produce. Chlorpropamide appeared to be embryotoxic in mouse embryos in culture.^{53–55} There is paucity of studies that have been performed to evaluate second- and third-generation sulfonylureas and their associations with malformations.

Denno and Sadler⁵⁶ evaluated the effect of biguanides, using metformin and phenformin as embryotoxic agents at

concentrations equal to serum levels obtained in patients treated with the agent clinically. They found that phenformin is embryotoxic, whereas metformin is not, suggesting that metformin is also the safer drug during pregnancy in patients with non-insulin-dependent diabetes mellitus. However, it should be noted that in the present study, metformin was not without adverse effects since it produced a delay in neural tube closure and also reduced yolk sac protein values at two different concentrations. While delayed closure of the neural tube may not have resulted in gross morphological abnormalities, it was not possible to assess subtler alterations that might result from such a delay using the culture system.

Shepard⁵⁷ and Schardein⁵⁸ reported that metformin did not appear to be a major teratogen because <0.5% of the rat fetuses in mothers administered 500–1000 mg/kg developed anophthalmia and anencephaly. However, evidence of embryo toxicity was evident with higher doses of the drug. Since animal studies are not conclusive about the safety of the fetus regarding the association between drugs and malformations, additional research approaches are needed to determine drug transfer across the placenta and/or tests of fetal blood for evidence of the drug.

Unlike other species, the human placental barrier is composed of a single rate-limiting layer of multinucleated cells, the syncytiotrophoblasts. During the formation of the placenta, fetal tissues erode the maternal blood vessels to attain a closer proximity to the maternal circulation. Chorionic villi that contain fetal blood vessels infiltrate the maternal vessels and establish a sinusoid in which the villi are suffused by maternal blood.^{59–62} Animal studies addressing placental transfer (e.g., mice) will not necessarily be applicable in humans.⁶³

The characteristics of individual drugs will determine their placental transfer capability. These factors will include molecular weight, pK_a , lipophilicity, placental blood flow, blood protein binding, and elimination half-life.⁶² Although the cutoff for actual molecular weight passage across the placental barrier has not yet been accurately defined, it is generally agreed that molecular weights ≤ 1000 Da passively permeate across the placental barrier with sustained maternal blood concentrations.^{64,65} Glyburide has a relatively short elimination half-life time (6–8 hours) and an extremely high protein binding (99.8%) that results in minimal placental transfer. Furthermore, there is effluxing of glyburide by specific placental transporters (e.g., P-gP, MRP1, MRP3, MRP3, and BCRP) even against concentration gradients from the fetal to the maternal side.⁶⁶

The recirculating single-cotyledon human placental model is widely used to characterize the transport and metabolism of numerous drugs and nutrients. It is a reliable *in vitro* model for human placental transfer since it facilitates the study of intact human placenta independent of fetal metabolism. Experiments can be validated against known substances that freely cross the placenta.^{67–69} Using this model, we evaluated whether first- and second-generation sulfonylureas cross the placenta.^{28,70,71} Glyburide's molecular weight is 494 units (U); it is one of the largest

oral hypoglycemic or antihyperglycemic agents. Transport and metabolism of glyburide across the human placenta was investigated in which the following was found: (1) Virtually there is no significant transport of glyburide in either the maternal-to-fetal or fetal-to-maternal directions, with an average transport of 0.26% at 2 hours. These levels are threefold to eightfold higher than the therapeutic peak levels after a 5 mg oral dose in humans. In fact, when cord blood samples were tested using high-performance liquid chromatography (HPLC), glyburide was undetectable in these samples despite maternal plasma levels of 50–150 ng/mL. (2) Increasing the glyburide concentration to 100 times therapeutic levels did not alter transport appreciably. Equilibrium dialysis demonstrated that at least 98% of the glyburide was protein bound. (3) Glyburide is neither metabolized nor sequestered by the placenta. (4) The results of the study suggest passive drug transfer.

Another set of studies conducted in 1994⁷⁰ and 1997⁷¹ demonstrated that second-generation oral hypoglycemic agents, especially glyburide, do not significantly cross the diabetic or nondiabetic placenta. Fetal concentrations reached no more than 1%–2% of maternal concentrations. Although glipizide crossed the placenta in small amounts, this was significantly higher than glyburide. In contrast, tolbutamide diffused across the placenta most freely. Glyburide has not been demonstrated to be teratogenic in animal studies and is thus classified as a category B or C depending on the source.

The recommendation not to use oral hypoglycemic or antihyperglycemic agents because of an increased rate of anomalies was based on a retrospective study involving 20 patients with type 2 diabetes, all with hyperglycemia prior to conception (glycosylated hemoglobin [HbA1C] levels >8%).¹³ The existence of maternal hyperglycemia preconception makes it impossible to determine if the increased rate of anomalies in the study subjects was a result of the medication or of the elevated glucose levels.

In contrast, three studies have suggested that there is no association between oral hypoglycemic agents and congenital malformations. Towner et al.⁷² treated 332 patients with type 2 diabetes with oral hypoglycemic agents or insulin prior to pregnancy. They demonstrated, using a stepwise logistic regression, that the mode of therapy did not have an adverse significant effect, while the level of glycemia and maternal age were significant factors contributing to the rate of anomalies. Langer et al. demonstrated similar findings in a retrospective analysis of 850 women with type 2 diabetes exposed to different oral hypoglycemic agents, insulin, and diet therapy prior to and during the first trimester of pregnancy.⁷³ Again, it was the blood glucose and not the mode of therapy that had the net effect on the rate of anomalies. Koren,⁷⁴ at a National Institutes of Health and Food and Drug Administration conference, presented the results of eight studies and concluded that the use of oral hypoglycemic agents have no effect on the rate of fetal anomalies due to a very narrow confidence interval (CI) (odds ratio [OR] 1.0; 95% CI 1.05–1.85). Recently, two meta-analysis studies reconfirmed that there is no association between glyburide or metformin therapies and fetal malformations.

In a meta-analysis (comprised of 10 studies), no relationship was found between first-trimester exposure and anomalies, OR = 1.05 (0.65–1.70).⁷⁵ In another meta-analysis that included 8 studies, metformin treatment was associated with 57% protective effect (control 7.2% vs. 1.7% metformin treated). There is no evidence for increased risk for major malformations.⁷⁶

It remains unresolved if the treatment of type 2 diabetes with oral hypoglycemic agents will accelerate the rate of anomalies. On the other hand, is it an overreaction to condemn these medications? With existing data, care providers need to objectively present information to patients so that issues are addressed and informed decisions are made. Moreover, there should be diligence in separating data from studies of type 2 diabetes when considering the treatment for GDM. In the case of GDM, the issue of anomalies is simpler. Patients with GDM are diagnosed and enter therapy after the first trimester (after the organogenesis period). There then remains concern about potential fetal hypoglycemia and stimulation for macrosomia if the drug crosses the placenta. However, as previously discussed, glyburide does not cross the placenta in appreciable amounts, and metformin that does cross the placenta is not clinically associated with fetal malformation. Finally, we demonstrated⁴ that patients entering therapy after the first trimester have rate of anomalies comparable to patients treated with insulin and glyburide and similar to the rate reported in the nondiabetic general population. Others reported that in women with type 2 diabetes that were treated with oral agents prior and during organogenesis, no increased rate of fetal anomalies was found.

Is there an association between oral agents and maternal/neonatal hypoglycemia?

An example of a study used to generate the recommendation that there is an increased risk for neonatal hypoglycemia with the use of these drugs was a case report of three infants whose mothers received chlorpropamide and another mother of an infant given acetohexamide; another case report reported prolonged symptomatic neonatal hypoglycemia.^{11,12} Studies evaluating the existence of hypoglycemia using data from continuous blood glucose during a 72-hour monitoring period defined hypoglycemia as blood glucose <50 mg/dL for 30 minutes. In the insulin-treated patients, 4.2 ± 2.1 /day episodes and, for glyburide-treated subjects, 2.1 ± 1.1 /day episodes ($p = 0.03$) were reported. Asymptomatic hypoglycemia was identified in 63% of insulin-treated women and 28% for the glyburide-treated subjects. Overall, 84% of the hypoglycemic episodes were nocturnal.⁷⁷ Another study using self-monitoring blood glucose revealed that the rate of maternal hypoglycemia does not increase with the use of glyburide. In fact, women in diet therapy and with insulin treatment had higher rates of hypoglycemic episodes compared to women treated with glyburide.^{4,78} These findings were reiterated in two meta-analysis studies.^{79,80}

Are oral agents and insulin comparable in achieving glycemic control?

Since GDM is characterized by a milder abnormal glycemic profile and occurs 2–10 years earlier than type 2 diabetes, the use of oral hypoglycemic agents to treat GDM should prove to be even more efficacious. In addition, it is reasonable to expect that the success rate of therapy for patients with GDM should be $\geq 70\%$, as achieved in type 2 diabetes. Several retrospective studies and numerous randomized studies^{4,81–91} evaluated the use of glyburide or metformin in comparison to insulin. All found no difference in success rate between the drug therapies. Notelowitz⁹¹ studied the utility of tolbutamide, chlorpropamide, diet therapy, and insulin in a randomized study with a small sample size with relatively low power (each of the 4 arms contained 50 patients). There was no significant difference in perinatal mortality or congenital anomalies. Good glycemic control was defined as a blood glucose level <150 mg/dL. The percentages of the patients who achieved the targeted glycemic category (i.e., <150 mg/dL) are 80% of those using oral hypoglycemic agents or diet therapy and 36% of those treated with insulin. Eighty percent of subjects treated with oral agents or in diet therapy alone maintained targeted blood glucose levels <150 mg/dL. In contrast, only 38% of the patients with insulin treatment were able to achieve this level, probably due to poor compliance.

In Langer's study,⁴ glyburide was as effective as insulin, with 82% of the patients treated with glyburide and 88% of the patients treated with insulin achieving targeted levels of control. Four hundred and forty women in between 11 and 33 weeks gestation, with a singleton pregnancy, having GDM requiring treatment (a failed oral glucose tolerance test and a fasting plasma glucose level 95–140 mg/dL) were enrolled. The blood glucose profile characteristics prior to initiation of therapy were comparable for the glyburide- and the insulin-treated groups (114 ± 9 versus 116 ± 22 mg/dL, respectively). Patients were randomly assigned to receive either glyburide ($n = 201$; initial dose 2.5 mg orally, increasing by 5 mg/week up to a total of 20 mg) or insulin ($n = 203$; initial dose 0.7 U/kg subcutaneously three times daily, increasing each week as necessary) for glycemic control. Patients were required to measure glucose values seven times daily. The targets for glycemic control were a mean blood glucose level of 90–105 mg/dL, a fasting blood glucose level of 60–90 mg/dL, a preprandial blood glucose level of 80–95 mg/dL, and a postprandial blood glucose level of <120 mg/dL.

Both treatments caused significant reductions in blood glucose levels compared with levels measured at home for 1 week prior to initiation of treatment. Mean blood glucose levels in the glyburide group decreased from 114 to 105 mg/dL, whereas those in the insulin group decreased from 116 to 105 mg/dL. The percentages of the subjects who were able to achieve targeted levels of glycemia are 82% of those treated with glyburide and 88% of those treated with insulin. However, eight glyburide-treated women (4%) failed to achieve the desired level of control early in the third trimester and were transferred to insulin therapy. None of the patients developed severe symptoms of hypoglycemia.

However, in the insulin-treated group, a significantly higher rate of subjects had 1%–6% of self-monitoring blood glucose determination values <40 mg/dL compared to the glyburide subjects. The glyburide and insulin groups had similar rates of preeclampsia (6%) and cesarean sections (23%–24%). Neonatal outcomes did not differ significantly between the two groups. The glyburide and insulin groups had a similar incidence of large-for-gestational-age (LGA) infants (12% vs. 13%), macrosomia (7% vs. 4%), lung complications (8% vs. 6%), hypoglycemia (9% vs. 6%), admission to a neonatal intensive care unit (6% vs. 7%), and fetal anomalies (2% vs. 2%).

In another study of the use of glyburide in pregnancy, the level of compliance in women using glyburide therapy to achieve glycemic control was reexamined. The success of glyburide therapy was defined as maintaining fasting plasma level <90 mg/dL and 1-hour postprandial level <130 mg/dL. Approximately, 83% of the women achieved these goals with universal satisfaction with the mode of therapy.⁹²

Success in achieving targeted levels of glycemia will vary from study to study because of different doses, administration algorithms, length of therapy, type of patient (severity and ethnicity), and noncomparable groups (compliant versus noncompliant subjects). To date, there is no evidence that a diabetic medication will be able to maintain targeted levels of glycemic control in all patients. Several studies^{93–96} determined that 75%–84% success was achieved with the use of glyburide as a primary therapy. When patients on glyburide failed to achieve targeted levels of glycemic control and transferred to insulin therapy, failure rate was 54%–67%. Physician intervention can prevent avoidable failure by adequately adjusting drug dose or prescribing alternative treatment when the original therapy has failed; however, other factors are unavoidable and not subject to physician intervention, e.g., race, obesity, and disease severity.

The success rate of metformin compared to insulin or glyburide in achieving targeted levels of glycemic control is less well defined. Several randomized studies^{82–86,90,97–99} evaluated the need for insulin supplements in metformin-treated women. In these studies, the range of metformin failure was 14%–46%. In the Rowen study,⁸⁶ the range of insulin dose required was 22–81 units. Predictors of the need for supplemental insulin include higher BMI and fasting glucose on the OGTT and earlier gestational age at diagnosis. A randomized small-scale study (46 patients in each arm) found lower mean blood glucose in the metformin vs. the insulin group.⁹⁰ Silva^{82,83} compared the success rates of glyburide compared to metformin in other small randomized studies. They concluded that treatment of GDM with metformin or glyburide was comparable for both women and newborns. In contrast, Moore^{84,85} in a randomized study of metformin vs. glyburide found that the failure rate to achieve the glycemic target was 2.1-fold higher for the metformin group (34.7% vs. 16.2%, 95% CI 1.2–3.9). Finally, a higher rate of fetal macrosomia and metabolic complications was found in the metformin study⁸⁶ compared to the glyburide studies.⁴ The data suggest that glyburide may be

more efficacious compared to metformin as a treatment modality in GDM in both controlling the level of glycemia and decreasing complications related to glycemia. In one study,²⁶ the failure of metformin to achieve targeted levels of glycemic control was 53.8% for established diabetics and 28.6% in patients with GDM. Apart from a high incidence of neonatal jaundice requiring phototherapy, the infant morbidity in the metformin group was low. The rate of LGA infants was double the rate found in the authors' general population. However, the LGA rate was comparable in the metformin- and insulin-treated patients, approaching 20%. Finally, in this study,²⁶ the mothers of the three infants with congenital malformations in the metformin group initiated therapy in the third trimester. Another study by the same authors²³ compared patients treated with metformin and glibenclamide alone, and the combination of diet, metformin, and glibenclamide. Patients who failed the oral hypoglycemic agent therapy were transferred to insulin therapy. The incidence of LGA neonates (>90th percentile) was 15% (metformin), 27% (glibenclamide), 33% (combined therapy group), and 41% (failed oral insulin-treated group). The relative increase in the rate of LGA infants must be explained by the severity of the disease and the higher rate of poorly controlled subjects in the group with the combination approach and the group treated with insulin. Neonatal hypoglycemia is defined as <25 mg/dL: the overall rate of neonatal hypoglycemia was 11.5%, with the highest rates for the patients treated with glibenclamide, 27% and combination therapy (glibenclamide and metformin), 18%, and the lowest rate in metformin-treated patients, 5%. The high rate of neonatal hypoglycemia corresponds with a rate of LGA infants reported in Langer's study, suggesting that a significant number of their patients were in suboptimal glucose control.

Effect of obesity and disease severity on achievement of targeted level of control

Although glyburide and probably metformin are comparable to insulin in the success of achieving targeted levels of glycemic control, the question remains if this comparison will hold true along the severity spectrum of GDM. We evaluated this issue by stratifying women with GDM based on fasting plasma glucose. We demonstrated that there was no difference in the rate of success for insulin- and glyburide-treated patients. This relationship was obtained in over 85% of patients with a glyburide dose ≤15 mg. For both drugs, the success rate decreased with the increase in severity category of the disease. The incidence of LGA infants increased in direct relation to the severity of the disease for both drugs.¹⁰⁰ In regard to metformin, the relationship between severity level and success in achieving targeted levels of control is less clear. Some studies have demonstrated comparable levels of success, while in others, approximately 46% of subjects needed the addition of insulin to the metformin therapy.⁸⁶

Women with Type 2 diabetes, by definition, are in a higher disease severity level than patients with GDM

(fasting plasma glucose ≥ 126 mg/dL). The pregnancy exacerbates the disease (insulin resistance) making it even more difficult to achieve targeted levels of glycemic control. Therefore, these patients will benefit from immediate assignment to insulin therapy rather than diet alone or oral agent treatment.¹⁰¹ However, when we compared success in achieving glucose targets and adverse perinatal outcome, we found no difference between patients treated with glyburide or insulin.¹⁰²

Association between oral agents and breastfeeding

Breastfeeding has, in the past decade, gained popularity in the United States where it was traditionally less popular than in Europe. Women are encouraged and motivated to breastfeed because of purported health benefits to the newborn and the psychosocial variable of mother-child bonding.

From the pharmaceutical perspective, only when the drug level is $\geq 10\%$ is there a need for concern. Studies have shown that the infant metformin level was 0.28% of the weight normalized to maternal dose while glyburide showed no trace in breast milk. Therefore, both drugs are safe to use during breastfeeding.^{103–105}

Cost-effectiveness of insulin vs. glyburide

In nonpregnant subjects with type 2 diabetes, the use of a sulfonylurea drug as a second-line agent appears to yield glycemic control and quality-adjusted life years (QALYs) similar to those provided by similar agents, but at a lower cost, according to recent findings. In the study,¹⁰⁶ the researchers created a population-based glycemic control Markov model to mimic natural variations in HbA1C progression. The study's outcome measures were life years, QALYs, mean time to insulin dependence, and anticipated costs of medication per QALY from diagnosis, onset of diabetes complications, or death. They evaluated the following four second-line intensification regimens: metformin, sulfonylurea, and insulin, metformin with a DPP-IV inhibitor

and insulin, metformin with a glucagon-like peptide 1 receptor agonist and insulin, and metformin and insulin. They found that all treatment regimens yielded comparable life years and QALYs, regardless of glycemic control target. However, the regimen in which sulfonylurea was the second-line treatment accrued significantly lower cost per QALYs and had the longest time to insulin dependence. For all treatment approaches, an HbA1C goal of 7% resulted in higher QALYs vs. a goal of 8%. The study took into account concerns regarding severe hypoglycemia in association with sulfonylurea use. The study data suggest that a glycemic control goal of 6.5% or 7% (~ 135 – 150 mg/dL) will be sufficient to prevent hypoglycemia. However, this threshold is significantly higher than the threshold of <100 mg/dL needed to optimize outcome of pregnancy.

To date, a single study sought to evaluate the cost of insulin vs. glyburide therapy. The author included the cost of insulin, syringes, needles, alcohol pads, and the teaching required for patient insulin administration. For the glyburide patients, they calculated the cost of the medication and the cost of instructing failed glyburide patients in insulin administration. The outcome of pregnancy was not included in the calculation since the outcome was comparable between the two modalities. They concluded that glyburide is significantly less costly than insulin therapy resulting in an average savings of at least \$165.84/patient (based on wholesale drug costs).¹⁰⁷

Conclusions

Different oral hypoglycemic agents act via diverse mechanisms of action. These drug characteristics provide a more physiological approach to the treatment of type 2 diabetes and GDM. Furthermore, combination therapies will enhance the effect of these drugs on glucose metabolism (Figure 24.1).

In addition, a pill will generally be more acceptable than an injection. In addition, the use of oral hypoglycemic agents is more convenient, less costly to the patient in supplies,

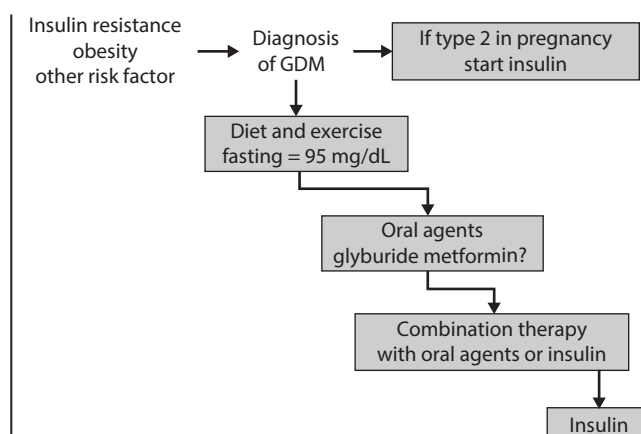


Figure 24.1 Usual sequence of interventions.

and less expensive in office infrastructure and staff. Insulin therapy involves daily injections that do not always result in optimal compliance by many women, and women in many developing countries cannot afford insulin therapy.

Today, sufficient data exist generated by several randomized and well-designed prospective and retrospective studies to support the use of oral hypoglycemic agents since they may have an even greater therapeutic effect in controlling glycemic levels. However, regardless of the mode of therapy, whole-patient care (glucose monitoring, education, diet

adherence, etc.) will determine the overall success in managing the disease and maximizing the quality of perinatal outcome. Thus, as food for thought, we need to remember the Hippocratic Oath (Orko V) that physicians swear to uphold: *Epi dhlhsei de kai adikihi eirxein*—"first, do no harm or cause injustice...." Withholding potential efficacious treatment because of "conventional wisdom" does not uphold the Hippocratic Oath. We need to remember that often it is not a question of right or wrong—it is more often a question of *what is more right*.

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25 The drug dilemma of oral antidiabetic agents in pregnancy: Metformin

Yoel Toledano, Moshe Zloczower, and Nicky Lieberman

Introduction

Metformin is the first-line oral treatment for type 2 diabetes mellitus (T2DM). A 2012 consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) suggested that both lifestyle intervention and metformin should be initiated as soon as diabetes is detected.^{1,2}

Mechanism of action

As a general rule, the effect of metformin is evident only in the presence of insulin. Moreover, it has several important effects:

1. Decreases hepatic glucose output.^{3,4} This is its major effect.
2. Increases insulin-mediated glucose utilization in peripheral tissues (such as muscle and liver), particularly after meals.
3. Has an antilipolytic effect that lowers serum free fatty acid concentrations. Correspondingly, substrate availability for gluconeogenesis is diminished.^{3–5} Overall, serum insulin concentrations may be mildly reduced in parallel with improved glycemic control.^{6,7}
4. Increases intestinal glucose utilization. This effect, demonstrated in experimental animals, is mediated by nonoxidative metabolism.⁴ This process generates lactate that can be metabolized in the liver as a substrate for gluconeogenesis.³ Consequently, hypoglycemia can be avoided, at least partly.

Exactly how metformin acts at the molecular level is not fully known, but might depend on the activation of the enzyme

AMP-activated protein kinase (AMPK). By this enzyme action, metformin probably lowers the blood glucose and lipid levels.^{8–10} Instead, metformin may inhibit gluconeogenesis by alternative pathways.

Efficacy

Monotherapy

Metformin is the first-line medical treatment in most patients with T2DM. Glycemic response to metformin is comparable to that achieved with sulfonylureas.^{3,4,6,7,11} Hence, glycated hemoglobin (A1C) and fasting blood glucose concentrations decrease by approximately 1.5% and 20%, respectively.

Compared with other oral agents, metformin has several advantages:

1. Has a benefit of modest weight loss or is at least weight neutral in obese patients.^{4,6,11} Conversely, many other antidiabetic medications, e.g., sulfonylureas and insulin, are related to weight gain.^{6,11}
2. Has no hypoglycemia risk generally.
3. Has lipid-lowering activity. Accordingly, serum triglyceride and free fatty acid concentrations are lowered.^{3,4,7}
4. Is related to a decreased rate of myocardial infarction and all-cause mortality¹² in overweight and obese patients with diabetes.

Combination therapy

Optimal glycemic control is frequently achieved with combinations of drugs. Metformin can be given in combination with sulfonylureas, glinides, dipeptidyl peptidase-IV (DPP-IV) inhibitors, alpha-glucosidase inhibitors, thiazolidinediones, insulin, and exenatide.

Side effects

1. Gastrointestinal reactions are the most common. Generally, 5% of patients stop metformin due to gastrointestinal side effects. They include anorexia, nausea, abdominal pain, diarrhea, and a metallic taste in the mouth.⁴ These reactions are typically mild and transitory. After discontinuation or dose reduction of the medication, the effects may reverse.
2. Decreases intestinal absorption of vitamin B12 in one-third of patients. Hence, serum vitamin B12 concentrations may be reduced. Megaloblastic anemia only rarely develops.¹³
3. Lactic acidosis: Incidence is very rare,^{14–16} up to 9 cases per 100,000 person-years of exposure.¹⁴ The mortality rate is very high. Symptoms are nonspecific. They include lethargy, hypotension, hyperventilation, anorexia, nausea, vomiting, and abdominal pain.

Predisposing factors are usually parallel conditions that are relative or absolute contraindications to the metformin therapy. The most significant predisposing factor is renal insufficiency. This category includes patients who are potentially at risk for developing contrast-induced renal failure, i.e., after receiving intravenous iodinated contrast material. Other risk factors include liver disease, alcohol abuse, past history of lactic acidosis, and, more rarely, heart failure. Simultaneously, this grave complication is generally presented in patients with shock or tissue hypoxia.^{4,17,18}

Taken together, patients should be recommended to stop metformin once they develop a predisposing factor for lactic acidosis. Hence, the risk of metformin-induced lactic acidosis can be significantly reduced. For example, it is recommended to discontinue metformin immediately prior to and for 48 hours after any exposure to parenteral iodinated contrast material administered as part of a radiologic procedure.

Dosing

The excretion of metformin is rapid in the urine.^{4,19} It is available as 500, 850, or 1000 mg tablets. Metformin should be administered with meals. The recommended starting dose is 500 mg once daily with the evening meal. The dose can be titrated and increased slowly per the glycemic response.⁴ The usual effective dose is 1500–2000 mg/day. The glycemic control is not significantly better with the maximum dose of 2550 mg/day (850 mg three times daily).¹ A long-acting preparation, an extended release tablet, is also available.²⁰

PCOS and metformin

Background

Polycystic ovaries syndrome (PCOS) was first identified and described by Stein and Leventhal as a combination of hyperandrogenism, menstrual disturbances, anovulatory infertility, and obesity.²¹ PCOS affects up to 15% of women

of reproductive age.^{22–24} Increased insulin resistance, i.e. subnormal biological response to normal insulin concentrations, and compensatory hyperinsulinemia play a key role in the pathogenesis of PCOS. At least 40% of women with PCOS are obese²⁵ and are more insulin resistant than weight-matched individuals with normal ovaries. On the other hand, women with insulin resistance commonly present with hyperandrogenism and reproductive abnormalities.²⁶ Moreover, obesity, mainly central or abdominal, as indicated by an increased waist to hip ratio, is correlated with reduced fecundity, menstrual disorders, and hyperinsulinemia.²²

Diagnosis

The diagnosis of classical PCOS in women of reproductive age is usually based on the Rotterdam criteria.²⁷ These criteria were accepted by the American Endocrine Society.²⁸ The basis for diagnosis is the presence of at least two of the following three criteria: androgen excess (usually hirsutism), ovulatory dysfunction (practically anovulation and infertility), and polycystic ovaries (by ultrasound). Congenital adrenal hyperplasia should be excluded before diagnosing primary PCOS²⁹ using basal or stimulated serum 17-hydroxyprogesterone.

Physiology

Hyperinsulinemia and hyperandrogenism represent a tangled web that reaches its greatest complexity in women with PCOS. The basis for the association between insulin resistance and ovarian hyperandrogenism is not known. Theories have proposed that hyperinsulinemia causes hyperandrogenism, or vice versa, or that some unknown third defect is responsible for both phenomena.³⁰ In addition, there is no clear correlation between the severities of hyperinsulinemia and hyperandrogenism.³¹ While excess androgen can cause a modest reduction of insulin sensitivity, the primary abnormality is probably insulin resistance, which in some way causes the ovarian abnormality. Insulin receptors, and the closely related receptors for IGF-1, are present in ovarian cells. Stimulation of these receptors increases androgen production.³² The administration of metformin or a thiazolidinedione, to reduce insulin resistance, lowers serum free testosterone concentrations and reduces cytochrome P450c17 (17-hydroxylase) activity in the ovaries.³³

However, there is currently no validated test for measuring insulin resistance in a clinical setting. Serum triglyceride concentration, the ratio of triglyceride to high-density lipoprotein (HDL)-cholesterol concentrations, and fasting insulin concentration are useful markers for identifying those who may be insulin resistant.³⁴ Optimal cut-points were identified as 130 mg/dL (1.47 mmol/L), 3.0 (1.8 SI units), and 109 pmol/L for triglycerides, triglyceride-to-HDL ratio, and insulin, respectively.³⁵ Sensitivity and specificity for the cut-points were 67%, 64%, and 57%, and 71%, 68%, and 85%, respectively. In large population epidemiology studies, simple ratios derived from fasting insulin and glucose (e.g., glucose to insulin ratios, homeostasis model

assessment of insulin resistance [HOMA-IR or HOMA]) have been extensively used. There are limitations to their use, including changes in beta cell function over time, lack of a standardized universal insulin assay, and lack of data demonstrating that markers of insulin resistance predict response to treatment. As a result, although indexes such as HOMA and QUICKI (quantitative insulin sensitivity check index) have been proposed and cut-points identified,³⁶ none are recommended for routine assessment of insulin resistance in the clinic.

Hyperandrogenemia can be stimulated by several mechanisms. First, abdominal obesity is associated with reduced levels of serum sex hormone-binding globulin (SHBG) and increased bioavailable serum androgens, which include free and albumin-bound androgens.³⁷ Second, obesity is associated with an increased testosterone production rate and a non-SHBG-bound androgen production rate of dehydroepiandrosterone and androstenedione.³⁸ Third, the combination of insulin resistance and increased LH secretion appears to stimulate ovarian androgen production.³⁹ Finally, elevated insulin levels inhibit hepatic synthesis of SHBG.⁴⁰ Furthermore, estrogen levels, particularly estrone, may also be higher in PCOS,⁴¹ although not participating in the hyperandrogenic state.

The molecular defects that cause insulin resistance have not been fully determined. In some patients, insulin resistance appears related to mutations in the insulin receptor gene that result in abnormal function of the insulin receptor.⁴² Accordingly, genetic defects leading to extreme levels of insulin resistance in women (e.g., those resulting from mutations in the insulin receptor gene) are typically accompanied by manifestations of PCOS.

Dysregulation of local follicle regulatory systems by androgens and other factors impedes normal follicular growth, resulting in follicular arrest at the 4–8 mm diameter size.³⁷ A dominant follicle (i.e., 18–25 mm in diameter) does not develop, and therefore, ovulation does not occur. Thus, the combination of elevated LH, hyperinsulinemia, ovarian androgen overproduction, and disruption of follicle growth produces the PCOS phenotype of oligoovulation and hyperandrogenism.⁴³

Associated morbidity

Abdominal obesity is the main metabolic abnormality in PCOS women. Women with PCOS are at increased risk for developing T2DM or impaired glucose tolerance (IGT). In a study of 122 obese women with PCOS, 45% had either IGT (35%) or T2DM (10%) by age 40.⁴⁴ Actually, T2DM and gestational diabetes (GDM) are two different variants for the same disease in different settings. They are considered as direct outcomes of the insulin resistance metabolic abnormality in PCOS. Moreover, they can lead to increased cardiovascular risk,⁴⁵ obstructive sleep apnea, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis.

Taken together, women with PCOS should be actively screened with fasting and 75 g oral glucose load for IGT and T2DM. A hemoglobin A1C (HbA1c) test is also accepted

as a more convenient screening tool.⁴⁶ The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay.⁴⁶

Treatment

Although it might be preferable to treat only insulin-resistant women with PCOS, there is currently no readily available and reliable test to evaluate the presence of insulin resistance. Thus, therapeutic interventions may be directed to specific symptoms of PCOS as control of hyperandrogenism and restoration of menstrual cyclicity and ovulation. Increasing insulin sensitivity and reducing insulin levels are considered as a more holistic therapeutic action.^{22,30} The treatments are either favorable or with no impact regarding the glucose homeostasis.

Therapeutic lifestyle change

Weight loss strategies with calorie-restricted diets and physical activity are the key to clinical improvement in overweight or obese PCOS patients. Indeed, they are likely beneficial for reproductive and metabolic dysfunction. There is no evidence that one type of diet is superior for weight loss. Weight loss is probably insufficient as a treatment for normal-weight PCOS women.²⁸

Hormonal contraceptives

Combined oral contraceptives are considered as the first-line management for the menstrual abnormalities and hirsutism and/or acne of PCOS.²⁸

Metformin

Treatment of T2DM is the only indication for metformin administration approved by the FDA. According to the 2014 ADA recommendations, metformin therapy for the prevention of T2DM may also be considered. It may be administered to patients with IGT, impaired fasting glucose (IFG), or an A1C of 5.7%–6.4%, especially for those with a BMI ≥ 35 kg/m² and women with prior GDM.⁴⁶ Nevertheless, it has been used “off-label” to treat or prevent several clinical problems associated with PCOS⁴⁷: oligomenorrhea, hirsutism, infertility, obesity, and early miscarriage. Next, we present the different therapeutic effects of metformin in patients with PCOS.

Metabolic effects: Metformin, compared with placebo, reduced plasma insulin by improving insulin sensitivity as measured by glucose clamp studies. Likewise, it reduced serum free testosterone and increased mean serum HDL cholesterol. Both the clinical and biochemical alterations were not correlated to changes in body weight. Also, they were sustained over a mean duration of treatment of 11 months in a follow-up observational study. However, there was no significant reduction in hirsutism despite the lower free serum testosterone concentration.³⁴ A meta-analysis

of 13 trials reported that metformin is associated with a reduction in blood pressure, LDL, and fasting insulin levels, when compared with placebo.⁴⁸

Gestational diabetes: The incidence of GDM is several-fold higher in women with PCOS than in the general obstetric population.^{49,50} Two observational studies suggested that metformin use was associated with a lower risk of GDM. However, this was not confirmed in a trial of 273 pregnancies among 257 women with PCOS who were randomly assigned to receive metformin (2000 mg/day) or placebo from the first trimester until delivery. No significant difference in the prevalence of GDM was detected between the groups (metformin 17.6% vs. placebo 16.9%).⁵¹

Obesity: At least 40% of women with PCOS are obese.²⁵ Metformin may be useful for achieving weight loss or potentiating weight loss by caloric restriction. A large clinical trial randomly assigned 150 obese women to receive weight reduction drugs (sibutramine or orlistat) or metformin (850 mg twice daily).⁵² After 6 months of treatment, all three groups had 9%–14% reductions in BMI. Thus, metformin treatment was associated with as much weight reduction as other anti-obesity medications. In another study involving obese women with and without PCOS, metformin (850 mg twice daily) plus a low-calorie diet (1200–1400 kcal daily) was superior to a low-calorie diet alone in facilitating weight loss.⁵³ Other investigators have reported similar results.^{54,55} One trial reported that higher-dose metformin (2550 mg/day) was more effective for weight loss than lower-dose metformin (1500 mg/day) in obese women with PCOS.⁵⁶ The dose-dependent effect was observed in women with a BMI between 30 and 37 kg/m², but not in those whose BMI was greater than 37 kg/m². Metformin appears to decrease caloric intake by suppressing appetite.⁵⁷ This effect may be independent of its gastrointestinal side effects.⁵⁸

Infertility: Metformin has not been proven to be endometrial protective but will restore ovulatory menses in approximately 50% of women with PCOS,^{34,59} although some studies report ovulatory rates from 23% to 90% in normoandrogenic anovulatory women.⁶⁰ This drug improves pregnancy rates when compared with placebo. Metformin and clomiphene together also improve rates when compared with clomiphene alone, but not when metformin is compared directly with clomiphene. Metformin does not improve live births whether it is used alone or in combination with clomiphene.^{61,62} Thus, the benefit of metformin appears limited regarding the improvement of reproductive outcomes in women with PCOS. However, it may prevent ovarian hyperstimulation syndrome (OHSS) in women with PCOS undergoing in vitro fertilization (IVF).⁶³

Dose and side effects: The optimum metformin dose for restoring ovulatory menses has not been determined. The two best studied metformin regimens are 500 mg three times daily and 850 mg twice daily. Some authorities

believe that women with PCOS who do not respond at these doses should be treated with 2000 mg daily.⁶⁴

Spontaneous abortion: The spontaneous abortion rate in women with PCOS is 20%–40% higher than the baseline in the general obstetric population.⁶⁵ Three studies in women with PCOS reported miscarriage rates of 62%–73% in pregnancies when metformin was not taken, and only 9%–36% of pregnancies in the same women under metformin.^{49,66,67} By contrast, in a meta-analysis incorporating 17 trials in women with PCOS taking metformin, with or without clomiphene, for ovulation induction, no effect of metformin was detected on the pregnancy loss risk (secondary end point⁵⁰).

Hirsutism: Although metformin may reduce serum androgen concentrations, it has limited benefit for the treatment of hirsutism.^{68–74}

In summary, the Endocrine Society recommended using metformin²⁸ in women with PCOS who have T2DM or IGT and failed lifestyle modification. For women with PCOS and menstrual irregularity who cannot take or do not tolerate oral contraceptives, metformin should be offered as a second-line therapy. By contrast, the use of metformin as a first-line treatment of cutaneous manifestations, as prevention of pregnancy complications, or for the treatment of obesity is not recommended. In addition, treatment of infertility should be initiated with clomiphene citrate (or comparable estrogen modulators such as letrozole) as the first-line treatment of anovulatory infertility in women with PCOS. Metformin usage is an adjuvant therapy for infertility and for OHSS prevention in IVF patients.

GDM and metformin

Among the antidiabetic agents, metformin and human insulin are classified as category B (no evidence of risk in humans). Yet, despite the inconvenience of injections, metformin is barely used in pregnancy. The American College of Obstetricians and Gynecologists (ACOG)⁷⁵ and the Endocrine Society⁷⁶ endorsed the use of metformin in GDM. Importantly, metformin crosses the placenta and could affect fetal physiology directly.⁷⁷ This fact is not considered as a disadvantage if fetal harm is excluded. Actually, a drug that improves insulin sensitivity in the mother and fetus has a theoretical advantage. This was the rationale of the Metformin in Gestational Diabetes (MiG) trial, as discussed later.⁷⁸

The drug has not been specifically approved by the FDA for treatment during pregnancy. Also, it was not recommended by the ADA.⁷⁹ Second- and third-trimester metformin treatment of GDM appears to be safe. One small retrospective cohort study⁸⁰ showed increased rates of perinatal loss and preeclampsia as compared with insulin treatment. Many other studies reported that metformin use during pregnancy is safe and effective,⁸¹ even in the first trimester.^{51,65,67,82–90} The only disadvantage may be limited effectiveness. Between one-quarter and one-half of women will need insulin to achieve glycemic targets.

The largest trial assessing metformin use in GDM is the Australian MiG trial.⁷⁸ Seven hundred and fifty-one Australian women with GDM at 20–33 weeks of gestation were randomly assigned to receive metformin (with insulin supplementation if needed) or insulin therapy. Perinatal morbidity was reported as the composite rate of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, prematurity, and low Apgar score. One-third of women in each group experienced composite morbidity. There were no serious adverse effects related to metformin treatment; however, almost half of the women using it needed supplemental insulin to achieve glycemic control.

Another two small randomized prospective, open-labeled, Finnish studies in GDM pregnancies examined the effectiveness of metformin compared to insulin in the prevention of fetal macrosomy as the primary outcome. Both concluded that metformin is possibly suitable for the prevention of fetal macrosomy, especially in lean or moderately overweight women developing GDM during late gestation. However, 20.9%–31.9% of the women randomized to the metformin arm needed supplemental insulin, more likely among older, those with considerable obesity, high fasting blood glucose or higher serum fructosamine concentration at diagnosis, early GDM diagnosis, and earlier need for pharmacological treatment.^{91,92}

The latest published study evaluated glycemic control in women receiving metformin or insulin for GDM. Lower mean glucose levels were observed in the metformin group.⁹³ Women using metformin developed less weight gain and a lower frequency of neonatal hypoglycemia. In the metformin group, 26.08% of women required supplemental insulin for glycemic control. Early gestational age at diagnosis and higher mean pretreatment glucose levels were identified as predictors of insulin need.⁹³

Metformin for GDM prevention

Although observational studies of metformin use in women with PCOS supported this hypothesis,^{89,90} a randomized trial among women with PCOS did not.⁵¹ In this trial, as in many other trials, women in the metformin group gained less weight during pregnancy than those in the placebo group.

Long-term outcome

Metformin crosses the placenta.⁷⁷ Indeed, in one study, cord arterial levels were twice as high as maternal venous levels.⁹⁴ Long-term outcome of fetal exposure to an insulin-sensitizing agent such as metformin is unknown. Notably, it is not even known whether the exposure is beneficial or harmful. Thus, caution is still warranted in its use during pregnancy. A 2-year follow-up study of the offspring in the MiG trial reported no difference in total fat or central adiposity between metformin-exposed and nonexposed offspring. However, there was an increase in subcutaneous fat deposition.⁹⁵ Whether this is beneficial or harmful remains to be determined.^{96,97} Because offspring of diabetic mothers may not manifest obesity until the age of 5–7 years,⁹⁸ longer-term studies are needed. Until such studies demonstrate

long-term safety, patients who are prescribed metformin should be informed of the existing uncertainties related to transplacental passage.

Postpartum prevention of T2DM in women with prior GDM

T2DM is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion. Abnormal glucose metabolism can be documented years before the onset of overt diabetes. Although the natural history of IFG and IGT is variable, approximately 25% of subjects with either will progress to diabetes over 3–5 years.⁹⁹ Individuals with additional diabetes clinical risk factors, including obesity and family history, are more likely to develop diabetes. The risk for T2DM is higher in women who have had GDM.^{100–103} These women have defects in both insulin secretion and insulin action, the severity of which correlate with the future risk of diabetes.^{100,101}

As GDM is a predictor of developing T2DM, it is also a predictor for developing cardiac disease and metabolic syndrome in both the mothers and the offspring. For example, higher birth weight (>4.0 kg) may be associated with an increased risk of diabetes.¹⁰⁴ Long-term follow-up by the family physicians and efforts to prevent T2DM are suggested by ACOG,⁷⁵ the ADA,¹⁰⁵ and the *Fifth International Workshop Conference on Gestational Diabetes*.¹⁰⁶

The goals of diabetes prevention are delaying the onset of diabetes, preserving beta cell function, and preventing or delaying microvascular and cardiovascular complications. In order to prevent the development of T2DM, the post-GDM patient should be perceived as a “prediabetic” patient.

The main principles for managing these patients are as follows:

1. Long-term intensive follow-up, including timely testing for fasting glucose and HgA1C.
2. Promotion of lifestyle changes, including healthy diet, weight control, and regular exercise.
3. Encouraging breastfeeding.
4. For those women in which lifestyle changes fail to improve glycemic indices, it is suggested to use medical treatment, mainly metformin.

All patients should be counseled on the benefits of weight loss and increasing physical activity. Different programs for successful compliance, including health coaches and psychological support, are recommended. Patients should also be encouraged to stop smoking.

Importantly, changes in lifestyle, including diet modification, weight loss, and exercise, slow progression of IGT to overt diabetes.¹⁰⁷ The Mediterranean diet appears to be associated with several health benefits, including diabetes prevention.^{108,109} There is no single definition of a Mediterranean diet, but typically it is rich in fruits, vegetables, whole grains, beans, nuts, and seeds; includes olive oil as an important source of

monounsaturated fat; and allows low to moderate wine consumption. There are typically low to moderate amounts of fish, poultry, and dairy products, with little red meat.

The benefit of exercise in preventing diabetes has been demonstrated in several studies.^{110–115} Weight reduction resulting from lifestyle intervention, i.e., combined diet and exercise aimed at weight loss and increasing activity levels, can improve glucose tolerance and prevent progression from IGT to T2DM.^{107,116} Moreover, breastfeeding is correlated with reduced blood glucose levels and incidence of T2DM among both women with a history of GDM and women in the general population.^{117–119}

Pharmacologic therapy may be helpful in preventing T2DM in high-risk patients (GDM) for whom lifestyle interventions fail or are not sustainable.^{120,121} Metformin is a pivotal therapy in this setting. To the best of our knowledge, there is only one randomized controlled trial of pharmacological therapy in women with prior GDM that considered diabetes prevention as the primary end point (the Troglitazone in Prevention of Diabetes [TRIPOD] study¹²²). In this study, T2DM incidence reduced from 45% to 20% (RR 0.45) with troglitazone versus placebo. Troglitazone is not marketed anymore due to the risk of fatal liver failure.

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26 Facing noncommunicable diseases' global epidemic: The battle of prevention starts in utero—The FIGO challenge

Luis Cabero and Sabaratnam Arulkumaran

Introduction

In the last few decades, different health organizations have highlighted the growing importance of noncommunicable diseases (NCDs) on population health. Noncommunicable diseases, also known as chronic diseases, are not transmitted from person to person, are not acute, and cannot be treated in a short period but generally evolve slowly and tend to remain lifelong. The four main NCDs are cardiovascular disease (including heart attacks and stroke), cancer, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma), and diabetes.

NCDs' impact on life expectancy

In its latest report, the WHO acknowledged the impact of deaths due to NCDs. NCDs were responsible for 36 million deaths every year. Of this death toll, nearly 80% (29 million) occurs in low- and median-income countries.¹ It was considered that NCDs are the leading causes of death in all regions except Africa, but according to the current estimates, by 2020 the largest increase in mortality from NCDs will be in Africa. Deaths from NCDs in the African countries are expected to exceed the sum of those caused by communicable and nutritional diseases and maternal and perinatal mortality. NCD would be the most common cause of death in 2030.¹

In addition, more than nine million deaths attributed to NCDs occur in people under 60 years of age, and 90% of these “premature” deaths occur in low- and medium-income countries. Cardiovascular diseases are responsible for most NCD deaths (17.3 million annually), followed by cancer (7.6 million), respiratory diseases (4.2 million), and diabetes (1.3 million). These four groups of diseases account for

about 80% of NCD deaths.¹ It must be emphasized that all of them share four common risk factors: tobacco consumption, insufficient physical activity, excessive use of alcohol, and unhealthy diet.

In terms of attributable deaths, the main NCD risk factor globally is high blood pressure (attributed to 16.5% of deaths worldwide¹), followed by consumption of tobacco (9%), increased blood glucose (6%), insufficient physical activity (6%), and excessive weight gain and obesity (5%).¹ The rapid increase in the number of overweight children is observed in the countries with low and medium incomes.

NCDs affect all age groups and all regions. Children, adults, and seniors are all vulnerable to the risk factors predisposing to NCD, such as unhealthy diets, physical inactivity, exposure to tobacco smoke, or excessive use of alcohol. These diseases are also favored by factors such as aging, rapid and unplanned urbanization seen in certain countries, and the globalization of unhealthy lifestyles. An example of such factor can be the unhealthy diet, which can be responsible for high blood pressure, increased blood glucose, hyperlipidemia, and excessive weight gain and obesity. Those factors are called “intermediate risk factors,” and they can lead to cardiovascular disease, one of the NCDs.

Impact of NCDs on national and global economy

NCDs threaten the progress toward the target of the Millennium Development Goals (MDGs) of the United Nations (UN).¹ Poverty is closely related to NCDs. It is anticipated that the rapid rise of these diseases will hinder efforts to reduce poverty in low-income countries, because of the increased family expenses for healthcare. Vulnerable and

socially disadvantaged people get sick and die earlier than people of higher social status, mainly because of the higher risk of exposure to harmful products, such as tobacco or unhealthy foods, and limited access to health services.^{2,3} In resource-poor settings, the healthcare expenses for cardiovascular disease, cancer, diabetes, and chronic lung disease, as stated, can quickly exhaust the resources of families and force them into poverty. The exorbitant costs of NCDs, particularly prolonged and expensive treatment, or the demise of the breadwinner, are pushing millions of people into poverty each year, preventing the progress of the country and the society. National economies are suffering considerable losses due to premature death or disability to work resulting from heart disease, stroke, and diabetes. For example, it is expected that India and China will lose about \$558 billion from their gross domestic production (GDP) between 2005 and 2015 due to premature deaths.⁴⁻⁶ In 2005, heart disease, stroke, and diabetes caused an estimated loss of \$9 billion in India and \$3 billion in Brazil from the GDP.⁷ A study commissioned by the World Economic Forum concluded that the world will sustain a cumulative output loss of \$47 trillion between 2011 and 2030 because of NCDs and mental illnesses, about \$30 trillion of which will be attributable to cardiovascular diseases, cancers, chronic pulmonary diseases, and diabetes.⁸

Combating NCDs

In many countries, the excessive use of alcohol and consumption of unhealthy foods are affecting both high-income and low-income groups. However, the former can access products and services that protect them from the major risks, while low-income groups are often unable to afford it.

To reduce the impact of NCDs on individuals and the society, we should apply a comprehensive approach that reinforces all sectors, including those related to health, finance, foreign affairs, education, and agriculture and planning, to work together to reduce the risks associated with NCDs, and to promote strategies and intervention to prevent and control them.

An important tactic to reduce NCDs is to reduce the risk factors associated with these diseases. Effective and low-cost solutions exist to modify common risk factors (mainly tobacco consumption, unhealthy diets and physical inactivity, and excessive use of alcohol) and to map the epidemic of NCDs and their risk factors.¹

Another option to combat NCDs is to introduce some essential high-impact interventions with the focus on primary care in order to improve their early detection and timely treatment. Evidence shows that such interventions are also excellent financial investment, since if introduced early they can reduce the need for more expensive treatments. These measures may also be applied in situations with different levels of resources. For maximum effect, the public policies have to focus on healthy lifestyles that promote prevention and control of NCDs and reorienting health systems to meet the

needs of people suffering from these diseases. However, one must acknowledge that low-income countries tend to have a low capacity for the prevention and control of NCDs.⁹

Developmental origins of health and disease

In recent decades, various research areas have suggested that events involved in normal fetal development could have long-term effects and influence health in adulthood.^{10,11} It appears that metabolic changes in utero can influence the physiological and structural patterns that “program” long-term health in adulthood.^{12,13} Early studies by Barker et al.^{14,15} in the 1980s established that the prevalence of some diseases in adulthood, such as atherosclerosis, high blood pressure (hypertension), stroke, type 2 diabetes mellitus, and dyslipidemia, is related to the intrauterine environment (“Barker hypothesis”). Moreover, the association has been reported between low weight and height at birth, with increased risk of subsequent development of diseases such as hypertension, metabolic syndrome, and stroke.¹⁶⁻¹⁸ Other studies have confirmed this relationship and currently are trying to reveal some of the mechanisms behind it.^{19,20} On an experimental level, for example, nutritional restriction during pregnancy has been shown to irreversibly affect the structure, metabolism, and function in some organs, “programming” the development of certain diseases in offspring.²¹ The result of this research is that today we can talk about the fetal origins of many adult diseases (Developmental Origins of Health and Disease [DOHaD]).²¹ Animal experiments and epidemiological observations in humans suggest that nutrition received in the intrauterine environment modulates the metabolic activity of various tissues in postnatal life.^{22,23} An important consequence of intrauterine caloric and nutrient restriction is the accelerated growth in the postnatal period.²⁴

In fact, during periods of development, certain epigenetic modifications are taking place that establish the parameters within which the tissue functions. It should be mentioned that the functional changes made by epigenetic influences need not be phenotypically (physically) visible in order to be significant; however, they usually have long-term health consequences. These functional changes cannot be reliably detected by conventional testing, are observed only when they match certain environmental contexts, and are likely to be initially masked by systemic effects.

This developmental plasticity is more important during periods in which the cells are differentiating and forming specific tissues, as happens mainly during pregnancy (for both mother and child) and during early childhood, puberty, and menopause. DOHaD hypothesizes that environmental exposures during critical periods of development may cause subtle changes in certain biological functions, although, practically invisible, they can increase the risk of disease and dysfunction later in life.²⁵

Some of the most striking evidence of developmental plasticity that were first discovered came from the analysis

of the consequences of prolonged periods of famine. Dutch conceived in the time of famine during the last two years of World War II were more likely to develop metabolic syndrome in adulthood.²⁶ Subsequent research has also confirmed these findings in Chinese famine victims.²⁷ In both groups, the offspring were more likely to have hypertension, glucose intolerance, and excessive weight gain.

Epigenetic programming

The discovery of epigenetic programming has provided a plausible explanation why and how nutritional characteristics during critical periods of life can have health manifestation much later. At present, there are a number of examples in animal models of how changes in the diet can directly influence the epigenetic machinery by inhibition of enzymes that catalyze the DNA methylation, by histone modifications, or by altering the availability of substrates for enzymatic reactions. These epigenetic alterations cause the expression or suppression of certain genes that can alter the phenotype, depending on the nature of the affected biological process. Epigenetic changes can both be transient²⁸ or persist for long periods of time.²⁹

Epigenetic phenomena are fundamental features of mammalian development that causes persistent changes in gene expression without altering the DNA sequence. In this way, epigenetic mechanisms shape the phenotype of a cell without changing the genotype. Although causality has not been fully established, epigenetics provides information on the possible in utero that may cause predisposition to diseases in adult life. During development, epigenetic mechanisms may undergo substantial changes caused by various factors. These changes affect genes that are essential for both the development early in life as well as later physiological functions in adult life. An important fact is that epigenetic modifications are stable during cell division and can be transmitted to the next generation. There is increasing evidence suggesting that exposure to nutritional imbalances or environmental contaminants—including metals, pesticides, persistent organic pollutants, and chemicals in drinking water, such as triethyltin, chloroform, and trihalomethanes—can cause changes in epigenetic mechanisms, and this could provide explanation for their effects on adult health.^{30,31}

Epigenetics, in this sense, can also be understood as a mechanism by which organisms can survive in an unpredictable and changing environment. The fastest adaptation to the environment comes from the immediate demand to maintain homeostasis—the processes by which the body maintains a constant internal environment in response to external changes, often increasing energy expenditure. These processes are governed mainly by hormonal and neural signals. The other end of the spectrum of evolutionary change is adaptive, i.e., long-term adaptations of species that are driven by genetic change and therefore resulting in survival or demise.

Epigenetics can insert influence by turning on and off the gene transcription. Transcription is the process by which an RNA copy of a gene is made, and this RNA copy then

governs the cell machinery for the production of a specific protein. The addition or removal of a methyl group to a gene is a way of influencing this process, if a certain gene can be transcribed into RNA and, therefore, whether or not to produce the corresponding protein. Thus, methylation in a group of genes may cause changes in many biological processes occurring in the body, and affect the metabolism, causing energy expenditure or conservation. This process could also be responsible for more specific aspects such as eye or skin color.

The discovery of noncoding small RNAs has opened a new field of microRNAs, which also play an important role in epigenetics by modifying gene expression posttranscriptionally.³² MicroRNAs indirectly affect translation of key factors or enzymes required for epigenetic processes in the nucleus.

What is also remarkable is that these changes in programming are largely functional. They include alterations in gene expression, protein levels, cell metabolism and differentiation, and the number of cells and their location. Functional changes are not necessarily identifiable as pathological, but due to the changes in gene expression, these can lead to dysfunction and disease in adulthood. In such case, they can be considered as markers of increased risk of NCDs. As already mentioned, the functional changes are not necessarily apparent at the time of birth and, in some cases, may require a particular environmental or physiological trigger in order to be revealed. For example, certain subtle changes in breast tissue can significantly increase the risk of tumor growth in middle-aged patients without children.³³ A clear positive association between breast cancer and higher birth weight, birth length, and placental weight was reported. Further epidemiologic studies have confirmed these findings. For females who weighed 3500–3999 g at birth, the adjusted odds ratio for breast cancer is 0.86. In comparison, in females with birth weight less than 2500 g, the adjusted odds ratio is reduced to 0.5.^{34,35} Another example (as found in famine situations) is that certain changes in some specific metabolic set points can only be established when some types of diet are predominantly used (this could be the reason that fast food, modern lifestyle, and certain chemical exposures are the perfect “recipe” for obesity).

The essential concept of “gestational programming” means that the nutritional, hormonal, and metabolic environment provided by the mother to the fetus could permanently alter the structure and the cellular responses of various organs and alter the expression of certain genes that ultimately affect the metabolism and physiology of the offspring. Moreover, these effects vary according to the period of development, and as such, fetuses and newborns (rapidly growing) are the most vulnerable.

The effects on programming can be immediate, for example, the deterioration of organ growth at a critical stage, while other effects are delayed and not apparent until later. In this case, the question is how the memory of the early events is stored and how it is expressed later, despite the continuous cell replication and replacement. This again could be mediated through an epigenetic control of gene expression, which involves modifying the genome without altering the proper sequence of DNA.³⁶

In addition, there is currently some debate on whether certain nutrients can also modify the programming of the immune system.³⁷ Certain dietary patterns increase the risk of altering the immune mechanisms along with metabolic dysregulation and increase the risk of a wide range of NCDs. Besides changes in the nutrient profile and their caloric load, diet-induced changes in the intestinal microflora may also be involved in the pathogenesis and may increase susceptibility to many chronic diseases. In this context, it is highly relevant that allergic diseases are one of the first NCDs that may appear. Preventive strategies can, in this sense, enhance immune and metabolic health.

It must be acknowledged that, to date, most of the research on epigenetic mechanisms induced by nutrients has focused on the identification of single specific genes that somehow limit the complete picture of nutritional effects on the entire epigenetic landscape. Using a genome-wide approach has the advantage and potential ability to discover the targets of certain novel epigenetic mechanisms, which are sensitive to a specific diet modification.

As observed in other studies of epigenomic associations, epigenetic mechanisms of allergic diseases constitute a major challenge to be studied in greater depth, i.e., whether epigenetic variation is the cause or consequence of the disease. However, clarification of the potential link between epigenetic changes in allergic diseases could offer new opportunities for diagnosis and/or therapy.

Also, our biggest challenge is to identify the stages in the life cycle where the epigenetic machinery is more sensitive to a particular dietary factor in relation to subsequent health outcomes, so that prevention strategies based on changes in the diet could produce maximum benefit. It is important to note that multiple and complex multisystem interactions require the implementation of an interdisciplinary approach to overcome the growing burden of NCDs.

NCDs, maternal morbidity, and MDG 5: FIGO's role

All this current knowledge allows us to conclude that the perinatal period is a golden opportunity for preventive measures aimed at reducing the impact of the epigenetic preconditioning of NCDs and thereby reducing the likelihood of developing the aforementioned diseases when the newborns reach adulthood. However, the critical window of development that offers some plasticity (or pluripotency) may vary from organ to organ with differing effects, depending on when the insult occurs and the stage of development of a particular organ.³⁸ Focusing on the preventive care of pregnant women has the potential to modify the epigenetic environment of the fetus. Prevention or the optimal treatment of obesity, diabetes, and chronic hypertension in future mothers interrupts the vicious cycle of epigenetic programming of the fetus not only in the current pregnancy but also in future pregnancies. Hence, the effort to provide adequate prenatal care, preventing or treating conditions affecting

fetal epigenetic programming, is probably the most effective strategy to control the expansion of this great pandemic of NCDs we mentioned earlier.

The International Federation of Gynecology and Obstetrics (FIGO) is a professional organization dedicated to the improvement of women's health and rights and to the reduction of disparities in healthcare available to women and newborns, as well as to advancing the science and practice of obstetrics and gynecology. The organization shall pursue its mission through advocacy, programmatic activities, capacity strengthening of member associations, education, and training. The FIGO has a vision that women of the world achieve the highest possible standards of physical, mental, reproductive, and sexual health and well-being throughout their lives. The values of the organization are those of innovative leadership, integrity, transparency, professionalism, respect for cultural diversity, and high scientific and ethical standards.

Traditionally, the FIGO's focus is on high maternal mortality ratio (MMR) in low-resource countries and measures to reduce it. Recently, there has been a reduction in maternal mortality to 350,000 maternal deaths annually, which represents a 34% decline. However, reduction of maternal mortality in sub-Saharan Africa is far below optimum for achieving MDG 5 target A: to reduce the MMR by three quarters. The Countdown to 2015 initiative (www.countdown2015mnch.org) has shown that only 5 of the 68 countries are on track to achieve this target. The leading causes of maternal mortality are preventable and include postpartum hemorrhage (PPH), preeclampsia, obstructed labor, infections, and other causes such as undernutrition, anemia, and unsafe abortion. NCDs such as diabetes, obesity, undernutrition, and anemia are responsible for maternal conditions that have an important impact on maternal mortality.³⁹ Diabetes (pregestational and gestational) can cause macrosomia, obstructed labor, PPH, and neonatal mortality (prematurity, respiratory distress syndrome, hypoglycemia, etc.). Ensuring optimal health during pregnancy and in the early childhood years not only provides the best chance for a healthy start but also reduces suffering and the cost to society of chronic diseases over decades of life. In this sense, the preconceptional state can be crucial. Many parental effects on the developing offspring occur even before pregnancy.

The FIGO is developing different programs to address these concerns. For example, the FIGO Saving Mothers and Newborns Initiative aims to increase women's access to new, cost-effective, and evidence-based technology for the reduction of maternal and newborn mortality in 10 low-resource countries in Asia, Africa, Latin America, and Eastern Europe. The FIGO works with communities and promotes utilization of interventions to reduce maternal and newborn morbidity and mortality. Another example is the FIGO Adolescent Sexual and Reproductive Health (ASRH) Initiative, which focuses on strengthening the capacity of FIGO member associations at the national level and promotes access to information and quality services in ASRH. The Leadership in Obstetrics

and Gynecology for Impact and Change in Maternal and Newborn Health Initiative is another program that has an impact on the diagnosis and treatment of NCDs. The FIGO received a substantial grant from the Bill & Melinda Gates Foundation for capacity building of member associations in eight low-resource countries in Asia and Africa. The project will enable member associations to play a leadership role and influence policy and practices in maternal and newborn health. Improving maternal and newborn health in low-resource countries by strengthening the role of national obstetric and gynecologic associations will help to achieve MDGs 4 and 5 to reduce child and maternal mortality and morbidity.

The close link between child and maternal health and the importance of early-life origin of NCDs requires that preventive and healthcare interventions related to such diseases are integrated into reproductive, maternal, and child health programs, especially at the primary health-care level.⁴⁰ Many of these preventive strategies are effective for reducing both maternal and infant mortality and later chronic diseases. In addition, it will also be important to demonstrate that cost-effective interventions are possible. It may be helpful to emphasize the benefits of an alliance bringing together new advocates to each cause. In general, the NCD field is not addressing maternal health, and the maternal health field has not established a place for itself in the push for greater attention paid to NCDs. We have a unique opportunity for a change and we should not miss it. Getting attention to the subject of DOHaD on the global scene requires buy-in from a global voice. The FIGO is such a voice.⁴¹

Professional training is accompanied by an improvement in performance indicators. There are many areas, especially in low-resource countries, in which training different levels of women's healthcare professionals can be improved, so that better outcomes can be achieved, especially with respect to maternal and neonatal morbidity and mortality. Strengthening communication with and among member associations and building the capabilities and capacity of those from low-resource countries through strengthening leadership, management, good practice, and the promotion of policy dialogues will enable societies to play a pivotal role in the development and implementation of projects and policies aimed at the improvement of care available to women and their babies.

The FIGO, aware of that responsibility and joining efforts with other agencies and companies, is making a big effort so that prenatal care programs are appropriate for prevention and treatment of the most common preconditioning factors, especially in low-income countries. The detection and treatment of anemia, gestational diabetes, nutritional deficiencies, decreased alcohol and tobacco dependence, consumption of addictive substances, etc. are measures of high therapeutic value and not only could decrease the immediate adverse effects on pregnancy (prematurity, macrosomia, PPH, intra-uterine growth retardation [IUGR], etc.) but also have effects in the medium and long term, with the decline of the NCDs and their corresponding impact on population health.

In this sense, there are three elements of great impact: (1) The detection and treatment of anemia is one element (note that in certain areas the prevalence in anemia in the pregnant women reaches 80%, resulting in maternal mortality from PPH, as well as fetal morbidity from IUGR and prematurity, not to mention the long-term effect on the possible emergence of NCDs). (2) The detection and treatment of diabetes is another element (in certain countries, it is prevalent in 25% of pregnant women, with its impact on fetal growth as well as the increase in maternal mortality by obstructed childbirth). Recall the increased risk for obesity, diabetes, and metabolic syndrome that these children present, if predisposing factors are not controlled in the early postnatal life. (3) Maternal nutrition, as already cited, is an essential element of prevention, since a change in the availability of nutrients causes a hormonal adjustment in the fetus to reset its metabolism, so that the newborn is prepared for further malnutrition. However, if not properly fed during the postnatal age, this can lead to metabolic alterations that make him or her susceptible to certain diseases in adulthood. It has been demonstrated that low birth weight, followed by an accelerated growth during childhood, is a risk factor for cardiovascular disease and/or type 2 diabetes mellitus.

Conclusion

The knowledge that certain processes in utero and in early childhood can affect the risk of developing NCDs provides an opportunity to enforce interventions during this critical time, when they have the greatest effect. Using appropriate protocols, healthcare providers can educate mothers about the risks of certain nutritional and environmental exposures and integrate health promotion on the agenda, as part of the social and economic development, and all this could motivate a substantial reduction in the risk of NCDs.⁴²

At the high-level meeting of the UN on the prevention and control of NCDs held in New York, United States, in September 2011, a four-by-four strategy was proposed. Priority efforts to prevent NCDs (diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease) mainly focus on four risk factors in adults: poor diet, physical inactivity, smoking, and alcohol consumption. Although paragraphs 26 and 28 of the Political Declaration of the United Nations relate to certain aspects of prenatal nutrition, maternal diseases, and air pollution in households, these paragraphs describe only partially the full scope of the problem and the opportunities for intervention.^{43,44} This global health challenge has left no country untouched and bridges the division between rich and poor countries. We are all affected by the rising prevalence of chronic NCDs, wherever one takes a closer look.⁴⁵

The concept that the foundation for lifelong risk and susceptibility to numerous diseases begins in the womb and in early life—now referred to by the term developmental origins of health and disease—is not entirely new, but has only recently gained acceptance from the broader scientific community because of a swathe of good research

producing hard evidence of the link. The biological evidence is there, but the knowledge has remained confined to the academic environment and needs wider dissemination. To move from evidence to policy change requires a broad evidence based on proven solutions, including assessments of how much it costs, over how long a period of time, and what health benefits are expected. But policy is never dictated by hard evidence alone. It requires advocacy, persistence, and resourceful arguments. This is particularly important in the current global economic setting where there is fierce competition for limited resources, and the focus on maximizing health impact for the money spent is even stronger. Economic arguments make focusing on the link between maternal health and future health burden even more relevant and attractive. We know that provision of good services for maternal and child health is needed to stimulate development and reduce high rates of maternal and child morbidity and mortality; addressing

the DOHaD link presents another compelling reason to do so with more vigor. Evidence suggests that much more attention is needed on early life interventions to optimize nutrition and reduce exposure to toxic substances in order to reduce the increasing prevalence of NCDs.

Current and future health challenges demand new and changing competencies to form the basis for education, training development, and workforce planning. International developments in health promotion and evidence-based practice provide the context for developing health promotion competencies, standards, quality assurance, and accountability in professional preparation and practice. In addition to filling the training and development gap, there is a need to develop a comprehensive system for competency-based standards and accreditation to strengthen global capacity in health promotion, which is a critical element in achieving the goals for the improvement of global health.

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27 Links between maternal health and noncommunicable diseases

Anil Kapur

Introduction

The enormity of the health and economic challenges from noncommunicable diseases (NCDs) is now being understood as evidenced by the adoption of the Political Declaration on NCDs at the high-level meeting of the UN General Assembly in September 2011.¹ NCDs account for 36 million deaths annually (63% of global deaths), which is expected to rise to 52 million by 2030. Four out of five (79%) of these deaths occur prematurely in low- or middle-income countries.² In 2008, more than 1.4 billion adults aged ≥ 20 years (35%) were overweight; of these, 11% were obese (200 million men and nearly 300 million women).³ Since 1980, the prevalence of obesity has nearly doubled worldwide. Over a billion people live with high blood pressure. In 2008, the global prevalence of hypertension in adults aged ≥ 25 years was around 40%.⁴ Approximately 700 million people have dysglycemia (diabetes mellitus and impaired glucose tolerance [IGT]), which is projected to cross the billion mark by 2035.⁵ The World Economic Forum has, for 2 years in a row, rated chronic diseases among the five top threats to the global economy including in the low- and middle-income countries.⁶ According to the World Health Organization's (WHO) report on Women and Health, high blood pressure, high blood glucose, and overweight and obesity are the leading risk factors of death from chronic conditions in women >20 years of age, accounting for 25%, 39%, and 35% of deaths in low-income, middle-income, and high-income countries, respectively.⁷

Based on well-designed studies with interventions targeting adults at high risk, it is suggested that up to 80% of the NCD burden can be prevented by addressing the common risk factors of tobacco use and unhealthy diet including excessive use of alcohol and physical inactivity—a strategy proven in small initiatives but fraught with implementation difficulties at the population-wide level.⁸ When challenged with a problem of this magnitude, there is a need to look at innovative ways to address it. It is now well known that risk exposure to NCDs begins early—as early as the intrauterine life—and accumulates over many years. Does pregnancy and early life offer a window of opportunity for

intervening? Are there synergies between maternal health and NCD prevention that can be leveraged to the advantage of both?

NCDs impact maternal health

Adaptation of the Millennium Development Goals in 2000 brought about justifiable increased attention on maternal and child health (MCH) programs, especially in the developing world, given the pathetic state of MCH and its impact on human development. To best utilize resources, MCH programs have only focused on factors that directly impact maternal, neonatal, and infant mortality, resulting in improved access to maternity services and survival of “at-risk” mothers and their offsprings in many low- and middle-income countries. Unfortunately, this narrow short-term biomedical focus has failed to address the root causes and social determinants, and the very individuals saved continue to be vulnerable and are at highest risk of poor health and lower longevity due to NCDs striking in early adult life. In addition, NCDs, particularly diabetes, obesity, and hypertension, have significant adverse impacts on maternal health and pregnancy outcomes, and through intrauterine programming, the cycle of vulnerability to NCDs is repeated with increasing risk accumulation in subsequent generations, as will be explained in greater detail later. To improve both the short-term MCH outcomes and the long-term population health, NCDs must be addressed simultaneously alongside MCH.

Undernutrition, overweight and obesity, hypertension, and hyperglycemia are commonly associated with pregnancy; apart from poor pregnancy outcomes and causing considerable maternal morbidity and mortality, these result in further escalating the NCD burden through fetal programming.

Maternal nutrition

Worldwide, almost 870 million people suffer from chronic undernourishment⁹; 60% of these are girls or women.¹⁰ In most developing countries, maternal undernutrition is

endemic, contributing significantly to maternal morbidity, mortality, and poor birth outcomes including low birth weight (LBW), neonatal mortality, and subsequent childhood malnutrition. Annually, 13 million children are born with intrauterine growth retardation (IUGR), 112 million are underweight, and 178 million children ≤ 5 years suffer from stunting. Combined together, severe wasting, stunting, and IUGR-LBW are responsible for 2.1 million deaths and 91.0 million disability-adjusted life years.¹¹ The effect of undernutrition during pregnancy goes beyond one or two generations because of fetal programming and has tremendous public health and economic consequences. Balanced protein-energy supplementation in undernourished mothers during pregnancy results in 34% and 38% risk reduction for small-for-gestational-age (SGA) babies and stillbirths, respectively.¹²

Anemia, defined as hemoglobin (Hb) concentration < 110 g/L, affects more than 56 million pregnant women globally; two-thirds of these are from Asia.¹³ Nutritional iron-deficiency anemia is the most common reason and results in increased maternal and perinatal morbidity and mortality and long-term adverse effects on newborns.¹⁴ These include significantly higher risk of LBW, stillbirth, and preterm birth.^{15,16} Iron supplementation lowers the incidence of LBW (RR [relative risk] 0.80) but has no effect on the incidence of preterm or SGA birth.¹⁷

Severe anemia is associated with higher risk of preeclampsia compared to women with no anemia.^{16,18} Based on the data from the WHO Global Survey on Maternal and Perinatal Health, Zhang et al.¹⁸ concluded that both nulliparous and multiparous women with severe anemia had significant association with preeclampsia/eclampsia (aOR [adjusted odds ratio] 3.55 [95% CI [confidence interval] 2.87, 4.41] and aOR 3.94 [95% CI 3.05, 5.09], respectively), whereas only multiparous women with severe anemia were at increased risk of gestational hypertension (aOR 1.58 [95% CI 1.15, 2.19]).

On the other hand, high iron intake in pregnancy increases the risk of gestational diabetes mellitus (GDM) especially in nonanemic women, and routine iron supplementation should be reconsidered in this group of women.¹⁹ Higher prepregnancy intake of dietary heme iron^{20,21} and raised serum ferritin level^{22–24} are associated with an increased risk of GDM.

Studies from around the world show high rates of vitamin D deficiency among women of reproductive age and during pregnancy.²⁵ A systematic review in 2010 of first-trimester 25(OH) vitamin D level and adverse pregnancy outcomes concluded that the evidence of the association between vitamin D levels and pregnancy complications such as preeclampsia and diabetes is inconclusive.²⁶ A recent meta-analysis and systematic review including some new studies concluded that vitamin D insufficiency is associated with an increased risk of GDM, preeclampsia, and SGA and LBW infants.²⁷

Folic acid supplementation (450 μ g) before conception and throughout the first 12 weeks of pregnancy reduces the risk of neural tube defects (NTDs) in the offsprings. A Cochrane review in 2013²⁸ concluded that folate supplementation during pregnancy was not associated with

lower risk of preterm births, stillbirths, neonatal deaths, LBWs, predelivery anemia in the mother, or low predelivery red cell folate, although predelivery serum folate levels were improved. The review also did not show any impact of folate supplementation on improving mean birth weight and mothers' mean Hb levels during pregnancy compared with placebo treatment. The evidence from the review did not show any overall benefit of folic acid supplementation throughout pregnancy. Most of the studies included in the review were old (conducted over 30–45 years ago).

Vitamin B12 deficiency in women has been shown to increase the risk of infertility or recurrent spontaneous abortions. Starting pregnancy with inadequate B12 level may increase the risk of birth defects such as NTD and may contribute to preterm delivery, although this needs further evaluation.²⁹ B12 deficiency in pregnancy is associated with higher insulin resistance and higher incidence of GDM, as well as higher prevalence of type 2 diabetes (T2DM) at 5 years. Among B12-deficient women, the incidence of GDM increases with rising folate concentration.³⁰ Low levels of circulating B12 in mothers who are folate replete has been shown to be associated with "thin fat" offsprings with high prevalence of insulin resistance, suggesting a future risk for T2DM.³¹

Overweight and obesity

Complications of overweight and obesity during pregnancy include hypertensive disorders, coagulopathies, GDM, respiratory problems, and fetal complications such as large-for-gestational-age (LGA) babies, congenital malformations, stillbirth, and shoulder dystocia. Women being overweight in early pregnancy have a twofold to threefold increased risk for preeclampsia.³² Obesity is associated with increased risk of preeclampsia (aOR 4.46), induction of labor (aOR 1.97), postpartum hemorrhage (aOR 3.04), intensive care admission (aOR 3.86), GDM (aOR 7.89), thrombosis (aOR infinity), shoulder dystocia (aOR 1.89), C-section (aOR 3.50),³³ maternal infection (aOR 3.35), prolonged hospital stay (aOR 2.84), and instrumental delivery (aOR 1.17).³⁴

Maternal overweight and obesity (BMI > 25 kg/m²) is the most important modifiable risk factor for stillbirths in high-income countries, contributing to around 8000 stillbirths (≥ 22 weeks gestation) annually.³⁵ In developing countries, it is associated with a twofold to threefold increased risk of macrosomia, requiring institutional and assisted delivery, the lack of which results in significantly increased maternal morbidity and mortality.³⁶ A meta-analysis and systematic review of cohort studies of maternal BMI and risk of fetal death, stillbirth, or infant death concluded that even the modest increases in maternal BMI lead to significantly increased risk.³⁷ The number of women in their reproductive age who are overweight now exceeds the number of underweight women,³⁸ and if this trend continues unchecked, it may again reverse the recent nebulous gains in improved maternal health outcomes. Focusing on quality nutrition, physical activity, and general health of women especially during the reproductive years is an important public health

investment. Raising public awareness on the hazard of overweight and obesity, particularly among low- and middle-income communities undergoing rapid economic transition, is the need of the hour in relation to NCD risk and from a maternal health risk perspective.

Hyperglycemia

According to the International Diabetes Federation, there are now an estimated 382 million people (184 million women) with diabetes; in addition, about 316 million people have impaired glucose tolerance (IGT).⁵ By 2035, this number is likely to grow to over 592 million with diabetes and 471 million with IGT. The Asia Pacific region accounts for about half the global burden; China, India, Indonesia, Pakistan, and Bangladesh account for 185 million people with diabetes and figure among the top 10 countries with the highest number of people with diabetes.⁵ These very five countries also account for over half of the global live births (66 million/year).

Worldwide, one in six pregnancies may be associated with hyperglycemia, 84% of which involve GDM.⁵ In 2013, 16.8% of live births (21.4 of 127 million) were associated with hyperglycemia in pregnancy and 16% of these were due to overt diabetes in pregnancy. This does not account for pregnancies ending in spontaneous abortions, stillbirths, or intrauterine deaths that may have been associated with hyperglycemia, proven or otherwise. In high-risk groups, up to 30% of pregnancies may involve diabetes.^{39,40} The age-adjusted prevalence of GDM in the United States is higher than those of Asian or Pacific Island–origin women but more so (almost threefold compared to non-Hispanic whites) for migrant women born in the country of their origin.⁴¹ In Southeast Asia, one in four live births may occur in the setting of maternal hyperglycemia.⁵ A fact generally not known to or recognized by public health experts and policy makers is that 91.6% of cases of hyperglycemia in pregnancy occur in low- and middle-income countries.⁵ With limited access to maternal care, this may have major consequences for maternal health and a future burden of NCDs.

Increasing age is associated with higher prevalence of hyperglycemia in pregnancy, which is the highest (47.7%) among women >45 years. In general, the age of onset of diabetes is declining; at the same time, the age of marriage and childbearing is increasing; as a consequence, we may, in the future, see more women entering pregnancy with preexisting diabetes.^{42,43} Between 1999 and 2005, the prevalence of pregestational diabetes among pregnant women in southern California doubled.⁴⁴ In 2010, there were an estimated 22 million women with diabetes in the reproductive age group of 20–39 years; an additional 54 million in this age group had IGT with the potential to develop GDM if they become pregnant.⁴⁵ Thus, over 76 million women were at risk of their pregnancies being complicated with pregestational (overt) diabetes or GDM.

Several markers such as age; race/ethnicity; BMI; history of T2DM in first-degree relatives, GDM, macrosomia,

unexplained stillbirth, and spontaneous abortion in previous pregnancies; excessive weight gain; and the presence of polycystic ovary syndrome, metabolic syndrome, polyhydramnios, and suspected macrosomia during current pregnancy have been described to clinically identify women with high risk of GDM.⁴⁶ In practice, they fail to correctly identify more than half the women with GDM^{47–50}; thus universal screening for hyperglycemia during pregnancy must be the standard practice.

Hemorrhage, hypertensive disorders, obstructed labor, and infection/sepsis are among the leading global causes of maternal mortality.⁵¹ High blood pressure and gestational hyperglycemia are linked directly or indirectly to all of them; yet women are not routinely screened for hyperglycemia during pregnancy, and the diagnosis of GDM is often missed. Maternal mortality and morbidity attributable to diabetes in women may, therefore, actually be higher than current estimates.

Diabetes in pregnancy is associated with serious complications for both the mother and child. It has been shown that the negative consequences on the fetus and the mother increase linearly with increasing maternal blood glucose.⁵² Infants of mothers with pregestational diabetes have higher rates of malformation^{53–55}; good blood glucose control before conception and throughout pregnancy reduces these risks substantially.^{56,57} The major problems related to hyperglycemia during pregnancy are shown in Table 27.1.

A meta-analysis⁵⁸ shows that, overall, women with GDM have an increased risk of developing T2DM (RR 7.43, [95% CI 4.79, 11.51]). Within 5 years of the index pregnancy, the relative risk is 4.69, which more than doubles to 9.34, 5 years postpartum. The risk can be reduced or the onset of diabetes considerably delayed through preventive actions in terms of postpartum weight loss and adopting a healthy lifestyle.⁵⁹

Women with history of GDM also have higher prevalence of the metabolic syndrome and increased risk of cardiovascular disease (CVD).⁶⁰ Over a median follow-up of 12 years, women with GDM had higher risk of CVD (adjusted hazard ratio 1.66 [95% CI 1.30, 2.13], $p < 0.001$),⁶¹ more noninvasive

Table 27.1 Risks associated with hyperglycemia in pregnancy

Fetal risks	Maternal risks
Spontaneous abortion, intrauterine death, and stillbirth	Polyhydramnios
Lethal or handicapping congenital malformation	Pregnancy-induced hypertension and preeclampsia
Shoulder dystocia and birth injuries	Prolonged labor, obstructed labor, assisted delivery, and C-section
Neonatal hypoglycemia	Uterine atony and postpartum hemorrhage
Infant respiratory distress syndrome	Infections
	Progression of retinopathy

cardiac diagnostic procedures (OR 1.8 [95% CI 1.4–2.2]), simple cardiovascular events (OR 2.7 [95% CI 2.4–3.1]), and total cardiovascular hospitalizations (OR 2.3 [95% CI 2.0–2.5]) over a 10-year follow-up, after adjusting for age, ethnicity, and comorbidities such as preeclampsia and obesity.⁶²

Fetal environment contributes significantly to higher risk for diabetes than can be explained by genetic inheritance alone. Offsprings of mothers with GDM are four to eight times more likely to develop diabetes^{63,64} compared to siblings born to the same parents in a non-GDM pregnancy. Children born to obese or diabetic mothers are at higher risk of obesity and/or insulin resistance and T2DM during childhood,⁶⁵ adolescence,⁶⁶ and early adulthood.⁶⁴ Almost half (47.2%) of diabetes and obesity in the youth can be attributed to maternal GDM and obesity.⁶⁷ Population attributable risk for T2DM from GDM in certain populations may be as high as 19%–30%.⁶⁸ Maternal pregravid obesity combined with GDM leads to newborn hyperinsulinemia and increased fat mass until 6 weeks, whereas pregravid obesity alone does not, suggesting the pivotal role of GDM.⁶⁹ GDM creates a vicious cycle in which diabetes begets diabetes.

In view of the dramatic increases in obesity and diabetes, we should accept that screening, diagnosing, and treating GDM is worthwhile.⁷⁰ Skeptics, however, continue to question whether screening women for GDM is cost-effective. Most of the cost-effectiveness analyses in the past have not included long-term benefits⁷¹ or have been conducted in populations with a relatively lower burden of GDM; none of these were in low-income countries. A few recent studies including modeling studies show that GDM screening associated with postpartum lifestyle interventions for T2DM prevention is cost-effective in both high-income (United States, Israel) and low-income (India) countries.^{72–74}

Hypertension

Worldwide, high blood pressure with or without proteinuria is a major cause of maternal morbidity and mortality,⁷⁵ and hypertensive pregnancy disorders (HPDs) account for 10% and 15% of maternal deaths in low- and middle-income countries, respectively,^{76–78} as well as increased perinatal morbidity and mortality as a consequence of prematurity and poor fetal growth. Although the incidence varies in different parts of the world, overall nearly 10% of previously normotensive women experience abnormally elevated blood pressure at some point during pregnancy. There is no consensus about the definition of HPDs and several classifications have been proposed. The generally accepted broad categories are (1) gestational hypertension or pregnancy-induced hypertension (hypertension without proteinuria), (2) preeclampsia (hypertension with proteinuria), (3) chronic hypertension or essential hypertension (preexisting hypertension), and (4) chronic hypertension with superimposed preeclampsia. Preeclampsia/eclampsia have the highest impact on mortality and morbidity; these include renal or liver failure, clotting disorders, stroke, preterm delivery, stillbirth or neonatal death,⁷⁹ and C-section, especially emergency C-section.

Although most cases of preeclampsia can be managed successfully in well-resourced settings, severe preeclampsia is a life-threatening multisystem disease associated with eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), acute kidney injury, pulmonary edema, placental abruption, and intrauterine fetal death, all of which are difficult to handle in poor-resourced settings.⁸⁰

Several risk factors are associated with higher predilection for preeclampsia; these include nulliparity (RR 2.38; 95% CI 2.28–2.49), multiple pregnancy (RR 2.10; 95% CI 1.90–2.32), history of chronic hypertension (RR 1.99; 95% CI 1.78–2.22), GDM (RR 1.93; 95% CI 1.66–2.25), maternal age ≥ 35 years (RR 1.67; 95% CI 1.58–1.77), fetal malformation (RR 1.26; 95% CI 1.16–1.37), and mother not living with infant's father (RR 1.21; 95% CI 1.15–1.26).⁸¹ Preeclampsia risk increases with increasing prepregnancy BMI.⁸¹

HPD has long-term consequences for the offspring and the mother. Women with previous HPD have higher glucose, insulin, triglyceride, and total cholesterol levels after pregnancy.⁸² Women with HPD are at increased risk of cardiovascular and metabolic disorders, including a twofold increased risk for hypertension, a threefold increased risk for T2DM, and a 1.3-fold increased risk for dyslipidemia,⁸³ and these women may benefit from close postpartum monitoring, timely implementation of lifestyle modifications, and preventive measures for cardiovascular and metabolic risk reduction.^{82,83}

Offsprings of mothers with preeclampsia have higher blood pressure during childhood and young adulthood.^{84–86} The mechanism for the higher risk is not clear and may be genetic and epigenetic—a consequence of vascular or metabolic programming—and have shared family risks or a combination of these.

Maternal health impacts future burden of NCDs

Prenatal and early-life development through epigenetic programming influences the risks of NCD in later life,^{87–91} and this might be especially relevant to low-resource countries.^{91–94} The parent's health, particularly the mother's body composition and nutritional and metabolic status during pregnancy, determines fetal environment and affects risk for later NCDs.^{95,96} Ensuring a healthy pregnancy and a disease-free early childhood may be the most effective means of attaining the best future health and preventing NCDs. Fetal environment represented by the mother's periconceptional and gestational health determines whether one starts life with a health “advantage” or “handicap,” and it is on this “foundation” that NCD risk factors play out in later life. People starting life with a “health handicap” may be less able to withstand lifestyle risks and may be vulnerable to diseases early, compared to those starting with a “health advantage.” Similarly, lifestyle interventions in adult life to prevent diseases may have variable effects based on early-life programming.⁹⁷ The impact of life conditions on health—the social determinants of health—is

high on the global development agenda, and therefore, it is relevant to ponder that perhaps these social determinants get “hard wired” into the next generations’ genome through epigenetic changes. The recognition that early-life influences play an important role in the causation of chronic diseases does not imply an absolute deterministic process that cannot be overcome by later-life intervention; it only helps to point that the task becomes more difficult and expensive with lower chance of success when initiated later in life.

Focusing on short-term survival in terms of lowered maternal and perinatal morbidity and mortality to assess maternal health programs as has been the routine practice so far does not capture outcomes that have longer-term implications for adult health, life expectancy, quality of life, and accumulation of human capital.⁹⁷ Moreover, recommendations for nutritional interventions are frequently based on increasing birth weight, focusing on survival, gains in stature, or micronutrient status in the short term.⁹⁸ Longer-term follow-up data confirm the existence of only a narrow window of opportunity for interventions up to 24 months of age, and only limited benefit, or even harm, of feeding strategies thereafter.^{99,100} Small babies continuing to be malnourished and stunted during childhood and early adult life remain at relatively low risk for NCDs as long as they have sufficient sustenance for which they were programmed. With changes in living conditions as a consequence of economic development or urban migration, these individuals manifest diabetes, hypertension, and other NCDs at much lower BMI and central adiposity threshold.^{101,102} Studies on survivors of the Dutch^{103,104} and Chinese¹⁰⁵ famine show that individuals exposed to intrauterine undernutrition had significantly higher rates of diabetes in adult life, and the risk was highest in the subgroup that were relatively well-off in adult life. Similarly, LGA babies born to overweight/obese women with or without GDM are at high risk of obesity, diabetes, and metabolic syndrome in early adult life.^{63–69}

Developmental effects operate through a gamut of subtle influences that provide the fetus the cues (via the intrauterine environment) to predict the external environment it will be born into, as well as the flexibility to adjust its growth trajectory to match that environment. These cues, such as maternal under- or overnutrition (pregnancy weight gain), maternal obesity or GDM,^{106,107} or other maternal health insults like stress, or infections (malaria, tuberculosis, HIV/AIDS, etc.),^{108,109} create multigenerational cycles of disease¹¹⁰ through epigenetic changes. The mismatch between the predicted environment for survival programming and the actual environment in adult life may be a critical factor driving the NCD epidemic primarily through its effects on weight, blood pressure, and blood glucose.

In young women born small themselves, the physiological effects of pregnancy-induced weight gain, insulin resistance, and increased insulin demand may be exaggerated by the pre-existing insulin resistance and the lower ability to produce insulin as a consequence of their early-life programming, resulting in higher rates of GDM and/or pregnancy-induced hypertension. Seshiah et al.¹¹¹ reported GDM prevalence rates of 8%–10% among women of low socioeconomic status who

had a prepregnancy BMI of <19. Undiagnosed or poorly managed GDM sets off a cycle of future obesity and T2DM in their offsprings, and the cycle may repeat in subsequent generations with ever-growing risk accumulation until interrupted through appropriate preventive actions in the pre- and periconceptual period, during pregnancy, and in the postpartum period of the next generation.

The concept of fetal programming and its consequences is paradigm changing; it highlights that pregnancy offers a window of opportunity to provide maternal care services not only to reduce the traditionally known maternal and perinatal morbidity and mortality indicators but also for intergenerational prevention of several chronic diseases.⁴⁰

There are several barriers in achieving these objectives. These barriers related to GDM, for example, have been recently described in a systematic review and are briefly described.¹¹² Knowledge of and adherence to existing guidelines and procedures for screening and diagnosis seem suboptimal at best and arbitrary at worst, with no clear or consistent correlation to the health provider, health system, or client characteristics. Most women express commitment and motivation for behavior change to protect the health of their unborn babies, but knowledge about how to effectively make changes is missing. Compliance to recommended treatment and advice is seen as difficult and challenging, and precious little is known about health system or societal factors that hinder compliance and what can be done to improve them. When properly informed, immediately following a GDM pregnancy, many women express desire and intention to adapt healthy lifestyles to prevent future diabetes, but find the effort challenging. Adherence to recommended postpartum screening and continued lifestyle modifications seems even lower. Here, some healthcare providers, health systems, and client-related determinants and barriers have been identified.¹¹² Studies reveal that a sense of self-efficacy and social support is important for making and adhering to the changes. Noncompliance to screening or nonacceptance of diagnosis of GDM may be due to poor understanding of the consequences, or fear of stigmatization, and one needs to be careful how to address this in public health campaigns to avoid creating another platform for women to be blamed for adverse effects on their children’s future health.

Future direction for action and research

Having saved a mother with GDM and preeclampsia from dying of obstructed labor or postpartum hemorrhage and her macrosomic baby, or a mother with severe malnutrition and anemia and her LBW baby, what can be done to ensure their future good health and to prevent or significantly delay the onset of hypertension or T2DM? What should be done to ensure that a girl child born of such pregnancy is given due antenatal attention to prevent further intergenerational risk transfer? This requires transforming policy to integrate services for MCH, NCD care and prevention, and health promotion. It will also require cost-effective

investments in information technology, to identify and track these high-risk individuals to enlighten, empower, and encourage them to adopt healthy living throughout life as well as empower local health workers to support and follow their progress. Enrolling, monitoring, and tracking women during and after pregnancy and their offspring using information technology may be the most appropriate place to begin this health system transformation to break the ever-rising curve of chronic NCDs.¹¹³

There is a great need to carry out operational research to understand the facilitators and barriers to an integrated

health system response to jointly address the challenge of improving maternal health and addressing prevention of NCDs and developing scalable programs in real-life settings. In addition, developing tools and incentives to engage, enlighten, empower, and encourage “at-risk” mother-and-child pair and study of the impact of these actions over time on population health are required. Given the size of the problem, there is also a need to develop point-of-care easy-to-use diagnostic and prognostic tests to more accurately identify individuals with greater risk so as to deploy resources appropriately.

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28 Diabetic pregnancy in the developing world

Eran Hadar, Eran Ashwal, and Moshe Hod

Introduction

Diabetes and obesity, as components of metabolic syndrome and representatives of the noncommunicable disease spectrum, are incorrectly perceived as a unique problem of the developed world. In fact, they are emerging as a major health challenge in developing countries as well. Low-resource countries are experiencing a surge in the incidence of such diseases, traditionally associated with the lifestyle of high-resource countries, while limited funds are available to overcome this dilemma.

The issue of diabetes in the developing world is a relatively new problem. Hence, available data on the epidemiology, diagnosis, management, and outcome of diabetes in pregnancy, in such settings, are scarce. Although hyperglycemia is a well-established cause for adverse pregnancy outcome, studies of the racial and ethnic distribution of hyperglycemia in pregnancy have shown significant variation in its epidemiology and have not been systematically and thoroughly investigated in other aspects, such as screening, diagnosis, management, and maternal and perinatal outcome. Paucity of adequate data is the result of several factors: underdiagnosis due to lack of resource and facilities and multiple strategies for screening and diagnosis, of which some are poorly implemented and incompatible to low-resource rural areas along with poor compliance to diagnosis and follow-up. This results not only in an epidemiological bias but also leads to lack of proper diagnosis, inappropriate treatment, and an increased risk for diabetes-related adverse pregnancy outcome, for the mother and her infant (Figure 28.1). Moreover, the tremendous therapeutic progress in diabetes in general and during pregnancy in particular, in the developed world, during the last century has not reached to its full extent in low-resource countries, where resources for diabetes management are often lacking, resembling a situation reminiscent of the preinsulin era.

In this chapter, we shall review current information on the relevant issues of diabetes and hyperglycemia before, during, and following pregnancy, with an emphasis and focus on the special consideration in the developing world.

Epidemiology of hyperglycemia in pregnancy in the developing world

The epidemic of diabetes has a profound and universal effect on pregnant women, both prior and during pregnancy—type 1 and type 2 diabetes mellitus (T1DM and T2DM) and gestational diabetes mellitus (GDM), respectively. This holds true not only for high-income countries, which is well established in extensive research, but even more so in low-resource countries. Some low- and middle-resourced countries have the highest worldwide incidence of diabetes while in others the reported incidence is still relatively low. These data must be interpreted with caution, as partial and inappropriate screening and diagnosis may lead to bias. This occurs due to lack of recourses and facilities, especially in rural areas, leading to a significant underdiagnosis and underreporting bias, of the true incidence of T2DM and GDM.

Pregestational type 2 diabetes mellitus

The overall prevalence of T2DM is highly deviated in different ethnic groups and geographical regions. It is lowest in Africa (2.4%) and highest in Europe and North America (7.89%).¹ Even in the face of such low numbers, the incidence of T2DM in Africa has increased almost twofold from 1997 to 2010.² Recently published estimations anticipate that the number of individuals with diabetes will again double by 2030, reaching 366 million people worldwide, of them 61 million in Africa and 190 million in Asia.³

The World Health Organization (WHO) Ad-Hoc Diabetes Reporting Group reported on the prevalence of diabetes and impaired glucose tolerance (IGT) in a diverse patient population of reproductive aged women.⁴ They noted the lowest rates of diabetes (<1%) in Bantu (Tanzania), Chinese, rural Indian, Sri Lankan, and some Pacific populations. Low rates of diabetes (3%–5%) were reported in Italian women and in white, black, and Hispanic women in the United States. Rural Fijian Indian and Aboriginal Australian women had high rates of diabetes, reaching a prevalence of 7%. The highest rates were found in Pima, Papago, and Nauruan Indians (14%–22%). The prevalence of IGT was found to be under 3%

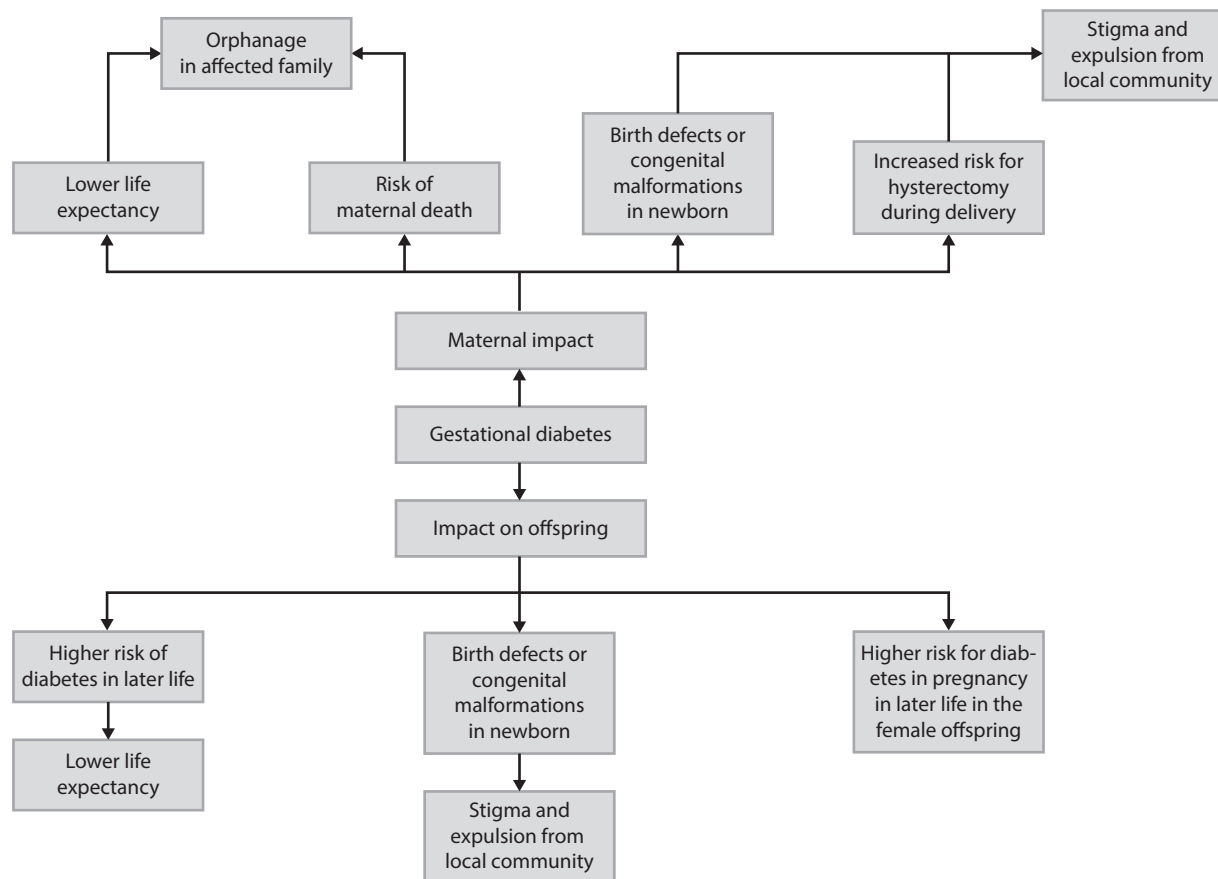


Figure 28.1 Maternal and neonatal consequences of gestational diabetes mellitus.

in Chinese and Malays and over 10% in black and Hispanic women in the United States, urban Indian, Tanzania, Pima, and Nauruan Indians and in other Pacific communities. The combined age-stratified rate of both diabetes and IGT ranged from 0% to 36%, with over 10% prevalence in one-third of the populations and beyond 30% prevalence in Pima and Nauruan Indians. Importantly, in several populations, the majority of cases diagnosed with diabetes were in fact undiagnosed prior to the survey. Thus, a significant proportion of patients with abnormal glucose tolerance will be missed without screening. This fact warrants special consideration for pregnancy planning, as it implies that a significant proportion of high-risk women will become pregnant without proper glycemic control prior to pregnancy, thus exposing themselves and their fetus to adverse outcome associated with pregestational diabetes, specifically congenital anomalies and pregnancy loss.

Gestational diabetes mellitus

The prevalence of GDM is linearly and positively correlated with that of T2DM, in any given population. Therefore, in correlation with T2DM, the incidence of GDM has also increased dramatically in the past decade in all racial and ethnic groups.⁵ The overall rate of GDM ranges vastly from 5% up to 25% of pregnant women, depending upon multiple risk factors, such as race and ethnicity, familial history, weight, height, age, and parity.⁶

The reported prevalence of GDM in the United States, as a representation of high-resource countries, ranges from 1% to 14%, with 2%–5% being the most commonly reported rate.⁷ Dooley et al.⁸ studied 3744 pregnant women who underwent universal screening for GDM. The patient population included 39.1% white, 37.7% black, 19.8% Hispanic, and 3.4% Oriental and others. The adjusted relative risk was increased in black (1.81, 95% confidence interval [CI] 1.13–2.89) and in Hispanic women (2.45, 95% CI 1.48–4.04). These findings were supported by others, showing that Asian women were more likely to have GDM than Caucasian women (31.7% vs. 14%, $p < 0.02$) despite their lower body mass index and socioeconomic status.^{9,10} Recent studies supported race as a risk factor, with similar findings of a high rate of GDM among Asians, Hispanics, Native Americans, and African Americans as compared to non-Hispanic whites.¹¹

Although closely related to race and ethnicity, from a geographical point of view, Guariguata et al.¹² in an extensive review concluded that 90% of the global GDM burden occurs in low- and middle-income countries, with a global prevalence of 16.9% and a disease burden of 21.4 million live births affected annually. The highest rate of GDM was found in Southeast Asia (23.1%) and the Middle East and North Africa (22.3%). In contrast to many countries in Asia and Latin America, where screening programs quantified the present problem, the majority of countries in Africa, mostly sub-Saharan Africa, lack the actual prevalence data

Table 28.1 Prevalence of gestational diabetes mellitus in selected African countries

Country	Description	Date	Prevalence (%)
Ethiopia	Rural, Northern Ethiopia	1999	3.7
Mozambique	Urban, Maputo	2002	7.3–11.0
Nigeria	Urban, six studies	2004–2012	1.0–13.9
South Africa	Urban and rural, four studies	1979–2011	0–8.8
Tanzania	Rural	2011	0

Source: Macaulay S, et al., *PLOS ONE*, 9(6), e97871, 2014. With permission.

of diabetes in pregnancy.¹³ Currently available epidemiological data from this region are summarized in Table 28.1, showing not only the wide prevalence but also the paucity of data coming from the 48 countries in sub-Saharan Africa.

The wide distribution variations in the prevalence of GDM by race and geography may be related to intricate associations between genetic factors affecting insulin resistance, lifestyle, diet, sociocultural factors, and healthcare access and utilization. As such, and due to the remarkably varied approaches used, different methods of screenings, various oral and intravenous glucose loads, and different diagnostic criteria, it remains unclear if this marked diversity represents true differences in the prevalence of GDM, or is simply biased. Understanding the racial, ethnic, and geographical disparities in GDM prevalence is a substantial first step toward improving maternal and child health, through improved diagnosis and better treatment.

Pathophysiology of hyperglycemia in pregnancy in the developing world

Several factors come into play, when attesting to explain disparities in the prevalence and outcome of diabetes in low-resource countries. This is a combination of both genetic and environmental influences.

From a sociocultural perspective, gender studies present the East African woman as a complex and dominant individual with a central role in society as mothers, workers, and members of families and communities.¹⁵ Women are focused and educated on their central role in reproduction. Accordingly, being childless leads to stigmatization and expulsion from the community.¹⁶ As a consequence, childbearing even in later stages of life is common, and this impacts the rate of diabetes in pregnancy.

Moreover, the impact of diabetes draws various social implications. In cases of diabetes prior to pregnancy, children may be born with birth defects, becoming customarily a female responsibility, with all the attendant implications. In addition, poor obstetric outcomes in such pregnancies may lead to a desire for “replacement” children. This, in turn, motivates high parity and its adverse sequel on the rate of diabetes. Both GDM and pregestational T2DM increase the

probability of intrauterine fetal death, macrosomia, shoulder dystocia, uterine rupture, and postpartum hemorrhage.¹⁷

Finally, it is well established that untreated GDM causes late-onset diabetes, leading to related complications in later stages of life and negatively impacting women’s life expectancy, morbidity, and mortality. GDM leads to a higher prevalence of diabetes in the offspring of mothers who were affected by diabetes in pregnancy and, in turn, burdens future female generations.¹⁸

From an environmental perspective, there is a complex interplay of obesity and malnutrition. Biological and environmental factors in rural areas of developing countries, in combination with malnutrition and infections, cause metabolic alterations distinct from those seen in developed countries.¹⁹ Malnutrition concomitant with physical work and iron and protein insufficiencies contributes to the high prevalence of low-birth-weight newborns.²⁰ Also, the pancreas appears to be sensitive to maternal anemia and infectious diseases. In both in vitro studies and human studies, a reduced number of pancreatic beta cells have been noted in children who were small for gestational age at birth, suggesting a reduced vascularization and replication rate of beta pancreatic cells.²¹ Fetal and early postnatal undernutrition can provoke metabolic adaptations that affect variables such as glucose uptake,²¹ insulin signaling,²² leptin levels,²³ and endocrine adaptations that affect the hypothalamic–pituitary–adrenal axis.²⁴ These changes mount to health outcomes such as coronary heart disease, stroke, T2DM, and the metabolic syndrome, all of which have been shown to be increased in low-birth-weight neonates.²⁵

On the contrary, obesity has a profound impact on hyperglycemia. The global trend of an increased prevalence of diabetes in low-resource populations, with the subsequent increase of GDM, is closely linked to higher rates of obesity and is related to lifestyle and dietary changes.^{26,27} In recent decades, the incidence of T2DM has dramatically increased worldwide due to changes in lifestyle, from those of hunters, gatherers, and farmers to a contemporary pattern mainly characterized by sedentary occupations and high-energy fuel resource intake.²⁸ It has been demonstrated that Africans, especially in urban settings, are experiencing rapid demographic and epidemiological transitions, changing diets and lifestyles encouraging urban drift and transnational migration. This is characterized by an enormous rise

in noncommunicable diseases—diabetes, hypertension, and cardiovascular diseases.²⁹ Currently, the highest prevalence of T2DM is found in populations that have undergone rapid alterations in lifestyle, such as Australian Aborigines, Native Americans, Pacific Islanders, and some migrant populations such as the Asian Indians.³⁰

Finally, there is an important role for genetic alterations. In 1962, Neel et al. proposed the “thrifty genotype” hypothesis as a preliminary explanation for these observations.³¹ In order to persist through centuries of evolution and in the face of the obvious and strong genetic selection against this condition, the diabetogenic genes must have conferred a survival advantage in times of nutritional deprivation; yet they were detrimental at times of adequate or overnutrition. In the 1980s, Barker et al.³² observed that the geographical distribution of heart disease was closely related to a person’s place and birth weight. This suggests that early life events can cause permanent changes in physiology that, depending on the environment, may later entail a predisposition to disease. In the 1990s, the “thrifty phenotype” hypothesis was suggested by Hales and Barker as a probable etiology of T2DM.³³ They claimed that adverse mechanisms of nutritional thrift on the growing individual are imposed by poor fetal and early infant nutrition. The thrifty phenotype hypothesis proposes that subsequent development of T2DM and the metabolic syndrome results from poor nutrition in fetal and early life, which produces permanent changes in glucose and insulin metabolism. During the period that the individual persists in the undernourished state, the physiological state is appropriately maintained. However, when the early adaptations that have been invoked to survive under restricted nutrient supply are later faced with conditions of affluence, the physiology is disturbed, sequentially leading to the occurrence of disease.³⁴ This phenomenon is particularly apparent in countries undergoing a rapid economic and nutritional transition, or in peoples migrating from poor to wealthy countries.³⁵ Observations in support of this assumption involve, for example, the increased susceptibility of Asians to diabetes³⁶ and of Africans to hypertension.³⁷

Yajnik et al. studied the body size and cord blood leptin and insulin concentrations in urban newborn (Pune, India) and white Caucasians (London, England). The Indian babies were much smaller than white Caucasian babies in all aspects apart from measurements of body fat and particularly central fat as judged by the subscapular skinfold thickness.^{38,39} They described these babies as having the “thin-fat” baby syndrome claiming it showed that the excess visceral adiposity in most Asian adults can be traced back to the neonatal phase. Also, cord blood insulin levels appeared to be higher, in Indian babies versus white Caucasian babies, and were correlated with subscapular skinfold thickness. Later in childhood, these “thin-fat” Indian babies have substantial impaired insulin sensitivity, which inversely correlated with birth weight.^{40,41} These studies, with subsequent support,^{42–45} provide solid data to confirm the claim that people living in developing countries are prone to suffer the greatest effects of early

programming, exposing them to a higher rate of diabetes and the metabolic syndrome.

Diagnosis of hyperglycemia in pregnancy in the developing world

Screening and diagnosis of diabetes in pregnancy appears to be more complex in low-resource countries, especially in rural areas. Several aspects need to be addressed in relation to the diagnosis of GDM and T2DM, which include financial, technical, and cultural barriers to appropriate diagnosis.

Screening and diagnosis

The dilemma of when and how to screen and diagnose diabetes, worldwide, as well as in developing countries—is continuously debated.^{46,47} In the developing world, inconsistency in detection mechanisms and screening methods of diabetes in pregnancy is being further magnified by the fact that most of the screening programs do not distinguish between GDM and undiagnosed T2DM—this may be solved with the adoption of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) principles for diabetes testing during pregnancy.⁴⁸ Moreover, simpler, cheaper, and accessible strategies for diagnosis of hyperglycemia in pregnancy need to be implemented uniquely for the low-resource countries:

Diagnostic thresholds—Defining cutoff glucose levels that are adequate for the particular setting of a developing country, considering the demographic shifts and local genotypes as a background determinant, remains a nonresearched challenge. Both diabetes in pregnancy and infectious diseases being highly prevalent in low-resource countries, along with malnutrition, potentially influence maternal metabolism, induce a catabolic state in the mother, and increase the risk of diabetic ketoacidosis and its complications during pregnancy.¹⁹ Basal glucose levels are most likely lower in pregnant women in low-income countries in comparison with their counterparts in high-income countries. Hence, in developing countries where a high prevalence of diabetes in pregnancy is assumed, outcomes could be more favorable when thresholds are set low, as more near-hyperglycemic pregnant women will be diagnosed with diabetes. However, taking into account financial constraints that such countries are facing and their need to focus on cost-effective, immediate lifesaving healthcare interventions, the cost implications of setting a low cutoff level may not be feasible, nor efficacious in most low-income countries. In many developing countries, specific target levels for the diagnosis and therapy of GDM and the consequences of their variation on the obstetrical outcome have not yet been formally evaluated.

Selective versus universal—Selective screening based on risk factors may be a cheaper alternative to laboratory testing. However, such schemes score poorly

in predicting GDM.⁴⁹ When selective screening is applied, it is estimated that approximately 16% of GDM women will be undetected.⁵⁰ The American Diabetes Association recommended selective screening for women belonging to ethnic groups with low prevalence of GDM. However, the lack of appropriate data on the prevalence of GDM in many low-income countries makes this selective screening nearly impossible. Universal screening for GDM in comparison to selective screening detects more cases and improves maternal and offspring prognosis.⁵¹ The cost analysis of universal screening when compared with risk factor screening showed only a negligible difference.⁴⁹ Thus, universal screening appears to be the most reliable and desired method for the detection of GDM, even in low-income countries.

Methods for detection—Universal screening as such must be simple and cost effective. Currently, the two-step procedure of screening with the 50 g glucose challenge test (GCT) and then diagnosing GDM based on the oral glucose tolerance test (OGTT) is not feasible in low-resource countries because it places a tremendous burden on the gravid women and jeopardizes their compliance. The two-step procedure requires the pregnant women to visit the antenatal clinic twice, and at least three to five blood samples need to be drawn. Alternatively, a single-step diagnostic procedure may be easier to implement. Even though the National Institutes of Health (NIH) consensus concluded that there is insufficient evidence to adopt a one-step approach, concerning that the adoption of a one-step procedure would increase the prevalence of GDM and the corresponding costs and interventions.⁵²

Some investigators have suggested low-cost alternatives for GDM diagnosis. Such innovative algorithms can certainly be used as alternatives when addressing diabetes in pregnancy in the developing world.⁵³ Agarwal et al.⁵⁴ evaluated fasting plasma glucose (FPG) as a screening tool for diabetes among 1644 multiethnic high-risk population. They concluded that FPG below 4.4 mmol/L rules out GDM with 94.7% sensitivity and that FPG ≥ 5.3 mmol/L rules in GDM with comparable sensitivity. Similar cutoffs of 5.1 and 4.4 mmol/L were tested on the hyperglycemia and adverse pregnancy outcome (HAPO) study population with similar results.⁵⁵ Such algorithms eliminate the need for OGTT in approximately 50% of the population, thus offering a simple low-cost algorithm for diagnosis, saving money, and reducing the need for a cumbersome laboratory procedure.

Obstacles to treatment of hyperglycemia in pregnancy in the developing world

Following diagnosis of GDM, proper pregnancy care, treatment, and follow-up should commence. There are several recognized obstacles to ensure such high-quality care in the

developing world,⁵⁶ which include lack of standard protocols, facilities, equipment, and the overall financing of health services; lack of appropriately trained healthcare providers, particularly female doctors, nurses, and diabetic educators; poor compliance to suggested care due to distance to health facilities, misperceptions of body size, weight gain/loss during pregnancy, and cultural issues of health negligence; lack of decision-making power among women; and superstitions as to healthcare in general and diabetes in particular.

Antenatal care and follow-up

Adherence to care, a lack of compliance because of poor availability, religious beliefs or superstitions, and fear of stigma can be expected. As families residing in rural areas do not have the financial means to pay for appropriate screening and/or treatment. Hence, most pregnant women will opt for a traditional pregnancy and birth attendant. In some rural areas, the patient with diabetes is considered as bewitched and as such might first consult a traditional healer or traditional birth attendant rather than seeking care from the medical health personnel.⁵⁷ Women residing in rural areas are much less likely to receive antenatal care than their urban counterparts. For instance, in the developing world as a whole, only one-third of rural women receive four or more antenatal care visits (WHO recommendation on the number of antenatal visits), in comparison to two-thirds of urban women.⁵⁸

Therefore, as for screening and diagnosis, low-cost and patient-friendly alternatives must be sought. Maiti et al.⁵⁹ from Kolkata, India, studied 50 GDM patients versus 31 controls employing a minimalistic approach for diabetes care. They included 2 weeks of nutritional care followed, if necessary, by twice daily regular human insulin, along with three fortnight glucose measurements at a laboratory and visits by the patient or family member, every 2 weeks. No differences were found between the two groups including perinatal mortality, macrosomia, shoulder dystocia, and birth injury. Although underpowered, this study shows that a simple and minimal approach may be adequate enough to ensure good pregnancy outcome. This approach reached 100% compliance versus lower rates of 60% compliance in other studies.

Diet and pharmacological treatment

Even in cases where elevated blood sugar levels are actually detected, the lack of financial resources poses a main barrier for adequate treatment, such as insulin or oral hypoglycemic agents.

Lifestyle changes such as adopting appropriate eating habits and engaging in regular physical exercise, which have already been proven to be cost effective in diabetes care, play an important role during and even before pregnancy. Such a strict diet may be impossible to implement in a low-resource setting, not to mention the impossibility to counsel for physical activity and weight loss during pregnancy. Obesity may be considered a desirable state in many low-income countries as it signals strength, wealth, affluence, and even beauty

in women. Being thin might be associated with being seriously ill, and therefore, women who are overweight might be reluctant to act on advice to lose weight to avoid diabetes or improve their diabetes control in pregnancy.⁶⁰

One of the major problems regarding diabetes care is the insulin itself. The high cost of insulin might not be affordable for some, especially for pregnant women from rural areas where health insurance schemes are absent. Furthermore, the appropriate storage of insulin supplies may be impossible, as temperatures in some tropical low-income countries can reach and go beyond 40°C, and refrigerators are not available.

Oral glucose-lowering agents are an alternative in low-resource settings, where patients might have a poor level of education and a lack of means to use insulin injections resulting in poor diabetic control.⁶¹ However, their use has not been studied in low-resource settings.

Technological availability

Women living in a rural low-resource environment are less likely to remember their last menstrual period. Thus, the estimation of gestational age is inaccurate and may not be dated properly due to lack of access to pregnancy care during the first trimester. Even when early pregnancy care is sought and reached, sonography is not available as a tool for pregnancy dating and for later follow-up and management. The lack of ultrasound even in referral centers throughout countries such as in East Africa poses tremendous difficulties for adequate pregnancy dating, monitoring of fetal well-being, and estimated growth throughout pregnancy.⁶² Also, the lack of access to even more basic tools, such as capillary glucose meters, remains difficult in rural areas.

Adverse outcomes due to hyperglycemia in pregnancy in the developing world

Hyperglycemia in pregnancy has a profound impact on maternal and neonatal outcome (Figure 28.1). Adequate information about maternal and perinatal morbidity and mortality (PNM) as a consequence of diabetes in pregnancy is scarcely reported.

In 2004, the WHO estimated that 529,000 maternal deaths occurred worldwide—251,000 in Africa (47%), 253,000 in Asia (48%), 22,000 (4%) in Latin America and the Caribbean, and approximately 2,500 (Less than 1%) in the developed countries.⁶³ In terms of maternal mortality rate (MMR), the world figure is estimated to be 4 to 1000 live births. Stratified by region, the MMR was highest in Africa (8.3:1000); followed by Asia (3.3:1000); Oceania (2.4:1000), Latin America, and the Caribbean (1.9:1000); and the developed countries (0.2:1000). A follow-up report estimated that maternal deaths worldwide decreased to 342,900 in 2008, with global MMR of 2.5:1000. The global MMR declined at a rate of 1.3% since 1990. During the years 1990–2008, the rates of yearly decline in the MMR

varied between countries, from 8.8% in the Maldives to an increase of 5.5% in Zimbabwe. In 2008, more than 50% of all maternal deaths occurred in only six countries, all low-income countries (India, Nigeria, Pakistan, Afghanistan, Ethiopia, and the Democratic Republic of the Congo).⁶⁴

Coetzee et al.,⁵³ from their departmental reports, found an overall PNM rate of 30/1000 births, while women with GDM and T2DM had PNM of 14:1000 and 70:1000, respectively. If left untreated, the PNM of women with GDM was 264:1000, and of women with T2DM it soared to 313:1000. For comparison, nondiabetic mothers who had received no prenatal care had a PNM of 94:1000. Hence, it is obvious that untreated diabetes poses a greater threat of PNM than having no prenatal care.

In addition to common diabetic complications such as retinopathy, nephropathy, and neuropathy in women with pregestational diabetes, infectious morbidity is significantly more frequent than in healthy women. There is a correlation between the frequency of infections and poor metabolic control.⁶⁵ Preeclampsia, which occurs in 20% of diabetic pregnant women—three times more frequent than in healthy pregnant women—significantly increases perinatal and maternal mortality and morbidity.⁶⁶ The major cause of maternal complications and subsequent deaths in low-resource countries as those in East Africa seems to be the delay in arrival at healthcare centers and hospitals.⁶⁷ Apart from the lack of financial means and living far from health centers, the low educational level often prevents a timely and potentially lifesaving presentation at health facilities especially for women in the rural areas.⁶⁸

Summary

There is a paucity of data available on the prevalence of GDM and pregestational diabetes in low-resource countries. Furthermore, the available data are derived mainly from the more accessible urban population while less data exist regarding populations in rural areas. In addition, the criteria for diagnosis are inconsistent, making comparisons difficult. The management of diabetes in pregnancy is a tremendously challenging task especially where existing resources are few, infrastructures are very weak, and the educational levels are low. More newborn infants are being exposed to the metabolic environment of diabetes during intrauterine development each year as a result of the changing incidence and demographics of diabetes and pregnancy. National governments along with the general public in the developing world must constantly be aware of the problems related to diabetes in pregnancy in order to establish appropriate programs including an approach to the diagnosis and therapy of diabetes in pregnancy. Within such programs and policies, the prevention and issues of accessibility and affordability of care have to be addressed. Simultaneously, education for healthcare workers must be implemented as they are able to identify groups at a high risk of diabetes and to contact women and educate them of the existence of diabetes in pregnancy and its impact on their offspring.

Awareness of diabetes at the primary care level, assisted by access to obstetrical and medical intervention when necessary, will decrease perinatal and maternal complications and diabetes-specific complications. Efforts to identify primary prevention strategies should be sought as secondary prevention as it is much more difficult to apply in low-resource countries. Women of reproductive age must be educated and empowered to seek antenatal

care. Improved healthcare knowledge will be associated with better family planning, better nutrition, and a better understanding of the threat that diabetes poses to pregnant women.

The development of programs and policies for the diagnosis and treatment of diabetes in pregnancy is a necessary key issue in attempting to prevent the diabetes complications in both the mother and her fetus.

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29 Managing diabetic pregnancy in China

Huixia Yang, Weiwei Zhu, and Rina Su

Introduction

Following the publication of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study,¹ the International Association of Diabetes in Pregnancy Study Groups (IADPSG)² formulated consensus guidelines for the testing and diagnosis of gestational diabetes mellitus (GDM). These have been adopted by the American Diabetes Association (ADA).³ The Ministry of Health (MOH) of China also recommended new testing and diagnostic criteria based on the IADPSG guidelines⁴, which became effective on December 1, 2011. The Chinese criteria agree with the ADA in 2013 that a diagnostic 75 g oral glucose tolerance test (OGTT) should be performed between the 24th and 28th weeks of gestation for all pregnant women not previously known to have diabetes. A diagnosis of GDM can be made if one or more of the following glucose levels are elevated: fasting ≥ 5.1 mmol/L, 1-hour ≥ 10.0 mmol/L, and 2-hour ≥ 8.5 mmol/L.

This is the one-step approach that the MOH has recommended to well-resourced medical institutions. However, in China, a formal OGTT may be difficult to implement in low-resourced rural areas. Therefore, and different from the ADA in 2013, the MOH has recommended a two-step approach under these circumstances. A fasting plasma glucose (FPG) can be used as a screening tool to reduce the number of OGTTs required. If the FPG ≥ 5.1 mmol/L after the 24th week of gestation, GDM can be diagnosed, and if < 4.4 mmol/L, GDM is unlikely. Women with FPG ≥ 4.4 mmol/L and ≤ 5.0 mmol/L will still require a OGTT. This approach will approximately halve the number of OGTTs required.⁵

Though MOH in China established the new diagnostic criteria of GDM (WS331-2011), standardized management to GDM has not spread in every area. A questionnaire survey was carried out in some regions to get the situation of the use of the new criteria and management to GDM at the beginning of the new criteria published (July–October, 2011).

The study subjects were the healthcare practitioners (HCPs) who attended the GDM training seminars in Tianjin,

Shanxi, Heilongjiang, and Guangdong and attended the national obstetrics conference. Nine hundred of 1190 questionnaires were collected as valid wherein the recovery rate was 75.6% (119 from Tianjin, 81 from Shanxi, 399 from Heilongjiang, 169 from the national conference). Four hundred and sixty-seven HCPs worked in tertiary hospitals (51.9%), 58 HCPs had a master's degree (23.1%), and 543 had a bachelor's degree (60.3%).

Use of the new GDM diagnostic criteria in the beginning

The criteria published by MOH (WS331-2011) adopted 75 g OGTT at 24–28 gestational weeks, and one of the three values matched the standard to get a GDM diagnosis. The percentage of HCPs who adopted the new diagnostic criteria was unbalanced in these survey regions. It was high in Shanxi and Guangdong, which were 63.0% and 53.1%, but Heilongjiang showed a very low percentage of 23.5% (Table 29.1).

Meanwhile, few HCPs adopted FPG 7.0 mmol/L in the first trimester to diagnose pregestational diabetes mellitus (PGDM), which was 33.3%.

At the hospital level, 205 HCPs from tertiary hospitals (46.6%) adopted the new criteria, which was higher than HCPs from other clinic instructions (194, 3.3%), but there was no statistical difference ($\chi^2 = 0.97$, $p > 0.05$).

Management of GDM

When a pregnant woman is diagnosed with GDM, medical nutrition therapy (MNT) and exercise should be the priority treatment. Most HCPs chose this option, with the highest rate in Guangdong (93.5%) and the lowest in Heilongjiang (77.8%). Though most HCPs chose MNT and exercise as priority, only about 20% doctors mastered MNT and could teach patients the knowledge of the food exchange method (Heilongjiang 19.8%, Guangdong 21.3%). Over 60% doctors heard of it but could not practice. About 80% HCPs would use insulin to treat GDM (Table 29.2).

Table 29.1 Use of new GDM diagnostic criteria in the beginning

	<i>n</i>	Constitution rate (%)
Tianjin	50	37.9
Shanxi	75	63.0
Heilongjiang	19	23.5
Guangdong	212	53.1
National	51	30.2
Total	407	45.2

Health education for GDM patients

The women with GDM has increased risk of gestational hypertension, preeclampsia, polyhydramnios, and urinary system infection in the short term and type 2 diabetes in the long term.⁶ If GDM in women is not well controlled, the fetus is at high risk for hyperinsulinemia, macrosomia, and birth hypoglycemia in the short term. The offspring also are at high risk for metabolic disorder, obesity, and early-onset type 2 diabetes in the long term.

There were 20.7%, 16.3%, and 15.9% of HCPs who did not realize the three long-term impacts separately.

Most HCPs would tell patients that GDM had influence to the mother and offspring in both the short term and long term. Meanwhile most of HCPs thought intervention would decrease the complications of mother and offspring. But about 10% doctors still considered intervention would have no effect on the complication of GDM (see Tables 29.3 and 29.4).

Knowledge of postpartum follow-up

In the survey, more than 95% of HCPs thought mothers with GDM and their offspring needed long-term follow-up. But in reality, only about 60% of them suggested the patients come for follow-up (Heilongjiang 50.6%, Guangdong 67.9%, and national 64.5%).

The suggested sections for follow-up were mostly the endocrinology department (about 60%) and obstetrical department (about 20%); see Table 29.5.

Management of GDM in China

The historical diagnostic criteria for GDM derived from the study of O'Sullivan et al.⁷ 50 years ago, which evolved into the national diabetes date group (NDDG) criteria and ADA criteria and is continuously used till now. The IADPSG recommended the new criteria based on the HAPO study while ADA accepted it in 2011. The MOH of China established the same new criteria on July 1, 2011. There is still some controversy about the new GDM diagnostic criteria. Walsh et al.⁸ found that the new diagnostic criteria for GDM would result in an increased rate of diagnosis of GDM and therefore increased surveillance of these patients. However, this treatment will not improve perinatal outcome, and we may now be diagnosing and treating a group of women without sufficient evidence of clinical benefit, while in this condition, the spread of the new criteria is still necessary.

Other nations also made a similar survey. For example, Akinci et al.⁹ made a study in Turkey and suggested that there is considerable variation in the clinical practice patterns

Table 29.2 Management of GDM

	HCPs chose MNT and exercise as priority (<i>n</i>)	Constitution rate (%)	HCPs chose insulin to treat GDM (<i>n</i>)	Constitution rate (%)
Tianjin	115	87.1	98	74.2
Shanxi	96	80.7	84	70.6
Heilongjiang	63	77.8	70	86.4
Guangdong	373	93.5	322	80.7
National	142	84.0	155	91.7
Total	789	87.7	729	81.0

Table 29.3 Patient education about the short- and long-term effects of GDM

	About effect to the mother	Constitution rate (%)	About effect to the offspring	Constitution rate (%)
Tianjin	126	95.5	126	95.5
Shanxi	114	95.8	114	95.8
Heilongjiang	73	90.1	72	88.9
Guangdong	382	95.7	367	92.0
National	156	92.3	154	91.1
Total	851	94.6	833	92.6

Table 29.4 Admit intervention effective to the complications of mother and offspring

	<i>n</i>	Constitution rate (%)
Tianjin	123	93.2
Shanxi	118	99.2
Heilongjiang	69	85.2
Guangdong	371	93.0
National	145	85.8
Total	826	91.8

of physicians, and they considered that an education program to enhance the clinical aptitude of physicians, particularly family physicians, in the medical management of GDM should be designed throughout the country. We conducted WDF 10-517 to train HCPs and patients to improve their knowledge regarding GDM. At the beginning of the project, the survey showed the following.

Unbalanced use of the new GDM standard in different areas

Over 50% of hospitals in Guangdong and Shanxi adopted the new standard, while only 30% did in Heilongjiang and Tianjin. A lot of hospitals still performed 50 g GCT. Some hospitals used the new standards only in high-risk pregnant women. For example, 31.8% of HCPs in Guangdong did not perform routine FPG test to pregnant women in the first trimester, while this percentage was 18.5% in Heilongjiang. This may be caused by less knowledge of doctors.

Update of GDM knowledge lagged behind seriously

The majority of doctors relied on textbooks or guidelines issued by the government. Fewer doctors obtained GDM knowledge through literature, such as in Tianjin and Shanxi, with only two and one doctor, respectively. Over 40% doctors had never heard of the HAPO study. Many doctors still rely on their knowledge of GDM during college, which is outdated. Less than 40% doctors knew the weight gain scope of diabetes during pregnancy. Update of GDM knowledge lagged behind seriously.

Poorly mastered medical nutrition therapy

The treatment of GDM is effective in reducing macrosomia (high-quality evidence), preeclampsia, and shoulder dystocia.¹⁰ MNT is the preferred treatment for GDM, wherein the majority of GDM patients control their blood glucose, thus making the doctor's guidance particularly important to patients. About 20% of doctors mastered MNT and could teach patients the knowledge of the food exchange method, while over 60% of doctors heard of it but could not operate, which reminds us that the most important thing to improve GDM management is to train HCPs, in every possible way, to master MNT.

Very low long-term postpartum follow-up rate

Carson et al.¹¹ collected 307 citations to identify system-based factors that could explain the broad variation in postpartum GDM testing rates and found that proactively contacting patients via phone calls, education programs, or postal reminders was associated with higher postpartum testing rates. Rather than working to identifying individual demographic factors, system-based approaches were associated with a larger potential impact and appear easily generalizable. Clinicians should think beyond individual habits and consider systematic approaches to improving testing rates.

In this study, lack of GDM knowledge prevented the doctors to educate and treat patients and value the importance of follow-up. In reality, they seldom asked the patients to come back for follow-up. Most doctors considered that the endocrinologists should be responsible for the follow-up of GDM patients, which reminds us that follow-up requires collaboration of both obstetricians and endocrinologists.

The pregnancy managements were unbalanced in different areas in China; thus we should make an appropriate management strategy based on local conditions. Maiti et al.¹² concluded that it may not be possible to provide access to Western standards of care to a vast majority of GDM patients in resource-constrained settings in developing countries, yet with minimal care delivered in a consistent fashion, it is possible to obtain excellent maternal and neonatal outcome. In China, for example, in Tianjin, pregnancy management in the first and second trimester is in community medical instructions; therefore, in this area, community capability should be strengthened when

Table 29.5 Chosen postpartum section for follow-up

	Endocrinology	Constitution rate (%)	Obstetrical	Constitution rate (%)
Tianjin	28	21.2	95	72.0
Shanxi	27	22.7	79	66.4
Heilongjiang	15	18.5	61	75.3
Guangdong	147	36.8	224	56.1
National	32	18.9	97	57.4
Total	249	27.7	556	61.8

GDM management is promoted. In other situations, training HCPs from tertiary hospitals should be considered, and tertiary hospitals should be in charge of improving their medical instructions, thereby developing a pattern where experienced tertiary hospitals are unified in managing locals with GDM.

Development of GDM management in China

Since the MOH criteria gained acceptance throughout China in 2011, the incidence of GDM has been estimated at 17.5%.¹³ The updated criteria and management in China have been published in 2014.¹⁴

With the support of the World Diabetes Foundation (WDF 10-517), national standardized trainings for obstetricians, professional nurses, and clinical nutritionists have been conducted in 16 different regions in China, totally 19,754 doctors and nurses have been trained, and 45 centers that focus on GDM screening and perinatal care have been

built. GDM management is promoted in a systemic pattern where 45 experienced tertiary hospitals are unified in managing locals with GDM.

As the incidence of diabetes and overweight in pregnancy has increased in China, a new project (WDF14-908) for diabetes management beyond pregnancy funded by WDF has been carried out from 2015. This project has mainly focused on prepregnancy, pregnancy care, and postpartum care at the hospital and community health service centers (CHSC) level for women with prediabetes and high risks of GDM. Like the FIGO initiative on GDM,¹⁵ the CHSC can support postpartum follow-up through child vaccination.

Patient education is important in the management of GDM. In China, a day-care outpatient clinic has been launched, where patients with GDM spend whole day and receive basic information on GDM, medical nutritional therapy, exercise advice, and self-monitoring of blood glucose, guided by professional nurses, clinical nutritionists, and physicians. The concepts of healthy lifestyle and blood glucose self-management promoted in the manual aim to prevent or postpone the development of type 2 diabetes later in life.¹⁶

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30 Gestational diabetes mellitus, obesity, and pregnancy outcomes

Harold David McIntyre, Marloes Dekker-Nitert, Helen Lorraine Graham Barrett, and Leonie Kaye Callaway

Introduction

Diabetes and obesity are frequently referred to as the “twin epidemics” of the modern world. The prevalence of both conditions is increasing worldwide, across high-, middle-, and lower-income countries.¹ Concurrently, the trend toward women having children at later ages, particularly in many developed countries, has led to an increasing prevalence of gestational and preexisting diabetes in pregnancy.² Gestational diabetes mellitus (GDM) and maternal obesity are both associated with a similar spectrum of risk for a broad range of pregnancy complications.³ This chapter aims to consider these risks together, analyzing their contribution to overall pregnancy outcomes from several perspectives: (1) underlying pathophysiology (common and discrete mechanisms), (2) combined clinical effects of obesity and GDM, (3) the current evidence base for various modalities of treatment with emphasis on the findings of randomized controlled trials, (4) population risks including the potential for prevention, and (5) current evidence gaps, evidence–practice gaps, and areas for future research. While recognizing that intergenerational effects are potentially of great importance, for reasons of space we are unable to consider these in detail in the current review.

Definitions

The definition of GDM has been controversial for almost the entire period since the term was first coined by Carrington.⁴ It is widely recognized that the hormonal changes of pregnancy can convert some women from a state of normoglycemia (in the fasting or post-glucose load state) to varying degrees of dysglycemia. However, from the very beginning of the study of GDM, it has been

recognized that women identified in pregnancy as “GDMs” carry a substantial long-term risk of permanent (generally type 2) diabetes (T2DM), and indeed, this risk formed the basis for the original diagnostic thresholds proposed by O’Sullivan and Mahan in 1964.⁵

In the modern context, the population prevalence of T2DM and lesser forms of dysglycemia including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) has increased dramatically among women of child-bearing age.⁶ Therefore, especially in high T2DM prevalence countries, many of the cases previously described as GDM under older definitions that spoke of “any form of hyperglycemia first identified in pregnancy”⁷ would likely have had abnormalities of glucose metabolism antedating pregnancy but only identified through pregnancy-related testing. Further, women with prepregnancy-undiagnosed T2DM have a much higher risk of severe complications in pregnancy⁸ and require urgent and intensive medical attention.

For this reason and for the purposes of the current chapter, we have adopted the recently developed International Association of Diabetes in Pregnancy Study Groups (IADPSG)⁹ or World Health Organization (WHO)¹⁰ definitions of GDM, which classify those women with more severe disturbances of glucose metabolism (which would be consistent with diabetes if noted outside pregnancy) into separate categories described as “overt diabetes” (IADPSG) or more simply “diabetes in pregnancy” (WHO). The relevant thresholds for glycemic measures defining GDM are shown in Table 30.1.

The definition of obesity is less controversial, with most authorities recognizing the WHO classification¹¹ while acknowledging both the imperfect precision of body mass index (BMI) as a measure of underlying adiposity and the fact that identical BMI thresholds are not uniformly applicable across all ethnic groups.

Table 30.1 Definitions of gestational diabetes and (overt) diabetes in pregnancy

Category	IADPSG	WHO
“Overt diabetes”—IADPSG	Fasting plasma glucose ≥ 7.0 mmol/L	Fasting plasma glucose ≥ 7.0 mmol/L
“Diabetes in pregnancy”—WHO	HbA1c $\geq 6.5\%$ Random plasma glucose ≥ 11.1 mmol/L (with confirmation)	2-hour plasma glucose ≥ 11.1 mmol/L after 75 g glucose load Random plasma glucose ≥ 11.1 mmol/L with symptoms
Gestational diabetes	Fasting plasma glucose—5.1–6.9 mmol/L	Fasting plasma glucose—5.1–6.9 mmol/L
Values obtained with a 75 g oral glucose tolerance test	1-hour plasma glucose ≥ 10.0 mmol/L 2-hour plasma glucose ≥ 8.5 mmol/L	1-hour plasma glucose ≥ 10.0 mmol/L 2-hour plasma glucose—8.5–11.0 mmol/L

Abbreviations: IADPSG, International Association of Diabetes in Pregnancy Study Groups; WHO, World Health Organization; HbA1c, glycosylated hemoglobin; mmol/L, millimoles per liter.

Pathophysiology of GDM and obesity in pregnancy

Pregnancy can be described as an allostatic state. Allostasis is the process by which the body responds to stressors in order to regain homeostasis or as achieving stability through change. Where homeostasis is the regulation of physiology around a set point, allostasis is the regulation of physiology to create a new set point. In an allostatic state, there is chronic activation of regulatory systems either due to some form of dysregulation/dysfunction of physiological processes or due to conflicting, competing, or opposing demands.¹² The allostatic load is the strain on physiology and regulatory capacity due to sustained activation of regulatory systems. This could also be defined as the regulatory load or metabolic load. However, continuous activation of any regulatory system or activation to a level outside of its norm will eventually lead to failure of the system. Both obesity and pregnancy can be considered allostatic states. In combination, they may lead to allostatic overload in which the compensatory systems may fail resulting in adverse pregnancy outcomes.

Outside of pregnancy, the brain is the main site for regulatory control in humans. In pregnancy, regulatory control is fundamentally altered due to the need for regulation of two organisms simultaneously. Additionally, regulatory control is partially allocated to the placenta in addition to the brain. In pregnancy,

circulating levels of glucose, insulin, cortisol, and leptin all increase. The physiological increase in maternal insulin resistance is an example of allostatic regulation: an adaptation of the maternal physiology to a changing environment (Figure 30.1).

Metabolism in healthy pregnancy

In early pregnancy, maternal metabolism is anabolic and results in maternal fat deposition. In healthy pregnancy, maternal insulin resistance increases throughout the second trimester with a peak in the third trimester due to secretion of placental lactogen. In normal women, insulin sensitivity decreases by 50%–60% from prepregnancy to late pregnancy.¹³ This decrease in insulin sensitivity (or increase in insulin resistance) is usually overcome by an amplification of insulin secretion from the pancreatic beta cells, ensuring normoglycemia throughout pregnancy.

The rise in insulin resistance contributes to shifting maternal metabolism from an anabolic state to a catabolic state. In the catabolic state, maternal metabolism becomes more reliant on lipids and ketones. This ensures an adequate glucose supply to the developing fetus. Insulin sensitivity is inversely correlated to maternal plasma free fatty acid levels.¹⁴ In addition to an increase in free fatty acid levels, other aspects of maternal lipid metabolism are also altered during pregnancy. Fat oxidation is significantly higher and a marked

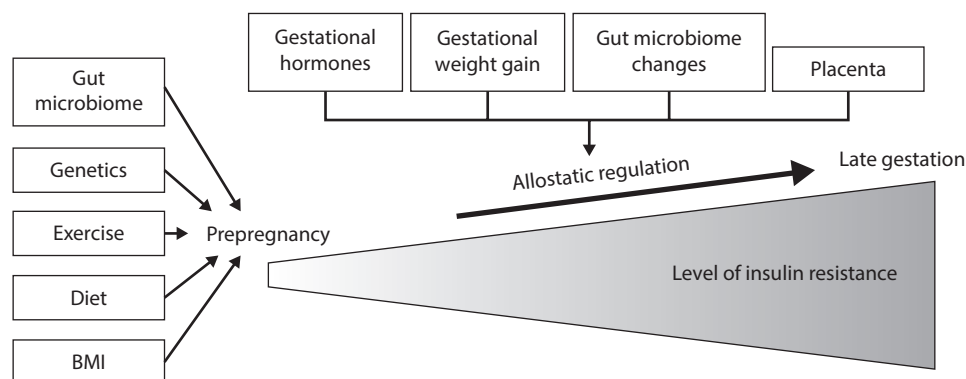


Figure 30.1 Factors influencing insulin resistance before and during pregnancy. Allostatic regulation maintains euglycemia in normal pregnancy.

hyperlipidemia occurs in late gestation. This includes an increase in the triglyceride content of very-low-density lipoprotein (VLDL), low-density lipoprotein, and high-density lipoprotein (HDL). Maternal plasma cholesterol also rises. The metabolic adaptations of healthy pregnancy are altered in pregnancies affected by GDM and/or maternal obesity.¹⁵

Glucose metabolism in GDM and obesity

In women with prepregnancy obesity, the pregnancy-associated rise in insulin resistance further exacerbates the high level of insulin resistance present in obesity. For many obese women, the additional rise in insulin resistance can still be compensated for by increased insulin secretion from the pancreatic beta cells. However, when the pancreatic beta cells cannot muster this compensatory increase in insulin secretion, hyperglycemia ensues and GDM is diagnosed. GDM is more prevalent in women with an increased prepregnancy BMI but can also develop in women with a prepregnancy BMI in the normal range. Additionally, the examination of maternal glucose profiles using continuous glucose monitoring devices showed that maternal glucose levels, while frequently below the diagnostic cutoff for GDM, are increased in obese women.¹⁶ Additionally, in obese women, adipokines including leptin and adiponectin, which are involved in lipid and glucose metabolism, are altered.

Lipid and adipose tissue metabolism in GDM and obese pregnancies

Decreased insulin sensitivity not only leads to increased availability of glucose but also of lipids. Obese women and women with GDM have higher triglycerides and VLDL cholesterol and lower HDL cholesterol levels than normal-weight normoglycemic women from early pregnancy onward.^{17,18} The subcutaneous adipose tissue of women with GDM shows lower protein expression for the insulin receptor substrate 1 compared with pregnant women without GDM, whereas the levels of insulin receptor substrate 2 are increased in fasting pregnant women compared with nonpregnant women independent of their glucose tolerance.¹⁴ Furthermore, it was recently reported that in adipose tissue from obese women with and without GDM, gene expression of many genes involved in fatty acid metabolism was decreased.¹⁹ This included fatty acid uptake and intracellular transport, triglyceride synthesis, lipogenesis, and lipolysis. In late pregnancy, inhibition of lipolysis by insulin through inhibition of hormone-sensitive lipase is less effective. Gene expression for transcription factors, including PPAR γ , that regulate lipid metabolism is also reduced in obese pregnant women with GDM.^{14,19} These studies show that insulin signaling in adipose tissue in women with GDM is altered and could contribute to the excess insulin resistance seen in GDM. Lower expression of PPAR γ in adipose tissue in pregnancy may be a reflection of the accelerated starvation with fasting late in pregnancy.¹⁴

Inflammation in obesity and GDM in pregnancy

In recent decades, the perception of adipose tissue has shifted from being regarded as a passive organ dedicated to fat storage to a metabolically active organ contributing to the regulation of whole-body metabolism through the synthesis and secretion of adipokines, cytokines, and hormones. Obesity and pregnancy are both states of chronic low-grade inflammation sometimes termed metabolic inflammation or “meta-inflammation.”¹⁸ In obese pregnancy, there is an increase in circulating proinflammatory cytokines, e.g., tumor necrosis factor alpha (TNF α), interleukin-6 (IL-6), and C-reactive protein.^{20,21} In obese pregnant women, the balance between proinflammatory and anti-inflammatory cytokines is altered, and this may contribute to increased maternal insulin resistance, for example, by differentially regulating phosphorylation of the insulin receptor and its substrates.²²

The placenta is an active endocrine organ, which contributes to the regulation of metabolism in both the mother and the developing fetus. The placenta synthesizes and secretes a large array of hormones, cytokines, and metabolic signaling molecules. Microarray studies of placentas from overweight women with GDM have shown increased gene expression for genes involved with inflammation and lipid metabolism but not glucose metabolism.²³ In obese pregnancy, the placenta and the adipose tissue both regulate maternal metabolism although their regulation is not coordinated.

As noted earlier, pregnancy is also a state of low-grade inflammation with the expression of proinflammatory cytokines from the placenta and the uterine epithelium.²⁴ The triggers for this inflammatory response are not well understood, but placental debris in the form of microparticles known as syncytiotrophoblast membrane microparticles (STBM)²⁵ or exosomes²⁶ as well as placental-derived signaling molecules may be implicated. Over time, the balance between proinflammatory and anti-inflammatory cytokines shifts toward the anti-inflammatory cytokines in normal healthy pregnancy.²⁷ In normal-weight women with GDM, levels of TNF α but not IL-6 are increased when compared to matched controls.²⁸ Furthermore, increased leukocyte counts in early pregnancy are predictive of the development of GDM, which is independent of BMI.²⁹

Infant weight and body composition

The Pedersen hypothesis, first proposed in 1952, states that macrosomia (e.g., a birthweight over 4000 g) results from fetal hyperglycemia and hyperinsulinism due to hypertrophy of fetal islets of Langerhans, which is the result of maternal hyperglycemia.³⁰ Macrosomia can occur even when maternal glucose control appears satisfactory and may be a result of increased maternal triglycerides and other lipids.^{15,17} Maternal obesity is associated with higher fetal fat mass³¹ as well as fetal insulin resistance.³² Maternal obesity is a predictor for fetal fat mass but not for lean mass.³¹ These results suggest that maternal obesity specifically

affects fetal adiposity rather than overall fetal growth. GDM unaccompanied by obesity is also associated with fetal adiposity.³³ Birthweight and fat-free mass are both correlated with insulin sensitivity in late gestation.¹³

Long-term influences

Maternal obesity doubles the risk for childhood obesity^{34,35} and is associated with metabolic syndrome in the offspring.³⁶ Similarly, children born large for gestational age (LGA) in the presence or absence of GDM also have increased risks of developing metabolic syndrome.^{36,37} In glucose-tolerant Pima Indian mothers, maternal glucose levels in the third trimester were strongly associated with increased risk of type 2 diabetes in the offspring.³⁸

These increased risks may partially be determined by a genetic background predisposing to obesity as well as by the postnatal environment related to the lifestyle of the family. However, some of the increase in risk may result from an altered intrauterine environment programming the offspring for later disease, as suggested by the Developmental Origins of Health and Disease (DOHaD) theory. Animal models have implicated altered epigenetic regulation affecting many regulatory and metabolic organs in the offspring including the brain, liver, pancreas,³⁹ and adrenals. In humans, long-term effects of the intrauterine environment have been reported with maternal undernutrition in the Dutch hunger winter study.⁴⁰ Placental function, which is a crucial determinant of the intrauterine environment, may therefore affect the health of the offspring long beyond its own lifespan.

GDM for the mother is associated with higher risks of hypertension, IGT, and hyperlipidemia, which are all components of the metabolic syndrome.³⁷ These increased risks are especially pronounced in women who were obese prior to falling pregnant.³⁷

GDM and obesity in combination

Many reports have attempted to dissect the relative clinical and population health importance of GDM and obesity in terms of their effects on pregnancy outcomes and later maternal and infant health. Separation of their associations is difficult, especially as the two conditions frequently coexist and obesity commonly lies on the casual pathway toward hyperglycemia. In some reports, women were not uniformly screened for hyperglycemia in pregnancy.^{41,42} In studies that provide evidence of glucose screening of their entire cohort, detailed analyses of the prevalence of GDM in overweight and obese women were not reported.^{43,44} In the vast majority of studies, treatment of GDM (but generally not specific treatment of obesity) is also likely to have confounded reported results. Fortunately, these problems are less of an issue when considering data from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study,^{3,45} as this study was blinded in terms of glycemia and did not provide specific interventions for obesity. The HAPO study showed that the associations of increasing maternal BMI and increasing

glycemia on pregnancy outcomes were similar. Both were associated with increased rates of the primary outcomes (LGA babies, primary cesarean section, clinical neonatal hypoglycemia, and neonatal hyperinsulinemia) and important secondary outcomes including fetal adiposity and preeclampsia. In general, the associations of maternal BMI with these outcomes tended to “plateau” in the highest categories, whereas those of glucose did not show this trend.⁴⁵ It is important to remember that, for ethical/safety reasons, women were unblinded from the HAPO study if their glucose levels exceeded the predefined thresholds, whereas no such limits were enforced for BMI.

The HAPO study group have also reported the combined associations of BMI and GDM with adverse pregnancy outcomes.³ Across the HAPO study, obesity was present in 13.7% of participants and GDM by the IADPSG criteria⁹ was present in 16.1% of those who remained blinded within the study. Only 25% of the women with GDM were obese. Compared to women with neither GDM nor obesity, the adjusted odds ratios for most pregnancy complications were increased both in women with obesity alone and in those with GDM alone. Preeclampsia appeared to be more prevalent in the “obesity alone group,” while excess fetal growth and fetal hyperinsulinemia were slightly more common in the “GDM alone group” than in the “obesity alone group.” The combination of GDM and obesity was clearly associated with a marked increase in the risk of pregnancy complications. These data are presented graphically in Figure 30.2. The HAPO study also presented data dividing their cohort firstly by BMI into normal and underweight/overweight/obese, with similar categorization applied to the composite oral glucose tolerance test “z” scores that were categorized as normal/intermediate/GDM. The definition of “intermediate” glycemia was selected to approximate the frequency of overweight in the HAPO participants. As shown in Figure 30.3, the frequency of LGA (adjusted birthweight >90th centile) increased across both axes, with the combination of GDM and obesity clearly carrying the highest risk.

In summary, the HAPO data clearly show that maternal BMI and glycemia have independent and essentially additive effects in terms of their associations with adverse pregnancy outcomes. In view of this, the relative “importance” of these factors is heavily influenced by the potential costs and benefits of preventative or treatment strategies.

Evidence base for treatment of GDM and obesity

There are now two well-designed large prospective randomized controlled studies that confirm that diagnosis and treatment of gestational diabetes has short-term benefits for both mother and baby.^{46,47} Women in the Australian (Crowther) study had early pregnancy BMIs ranging from 22.9 to 31.2 kg/m², and women in the intervention arm of the study had lower weight gain during pregnancy, with less macrosomia, less LGA, and lower rates of preeclampsia.⁴⁶ In the U.S. (Landon) study, the BMI at recruitment of women in the treatment arm was 30.1 ± 5 kg and control

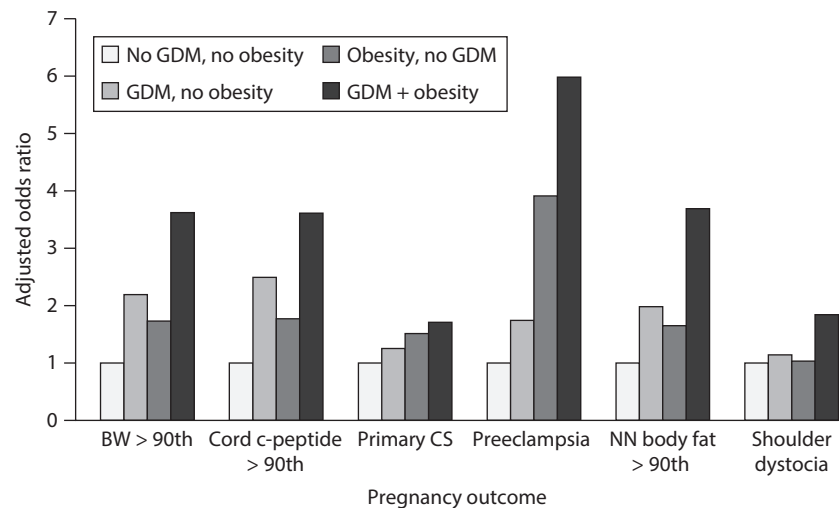


Figure 30.2 Fully adjusted odds ratios for selected pregnancy complications in the Hyperglycemia and Adverse Pregnancy Outcome study. The “No GDM, No Obesity” category served as the referent group for all comparisons. The other categories, as labeled, refer to GDM alone, obesity alone, and the combination of both factors. Odds ratios refer to “Model II” as explained in detail in the source publication, with full adjustment for potential confounders. GDM, gestational diabetes mellitus.

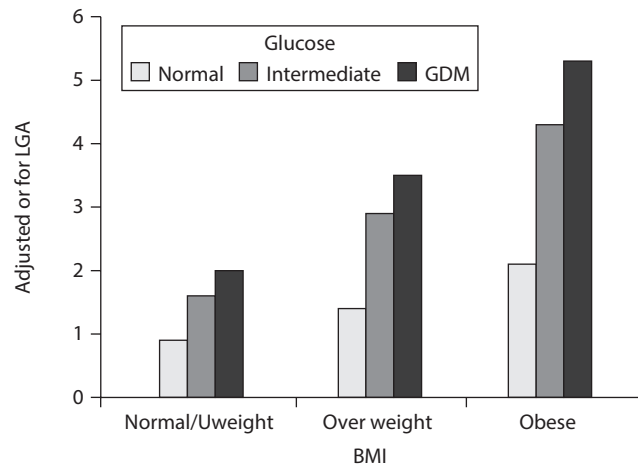


Figure 30.3 Fully adjusted odds ratios for delivery of a large-for-gestational-age (LGA) infant, characterized as birthweight >90th centile in the Hyperglycemia and Adverse Pregnancy Outcome study participants. The group with normal glucose levels and normal or underweight range BMI served as the referent group. The intermediate glucose group was defined according to their mean standard deviation (“z”) scores for the fasting, 1-hour, and 2-hour glucose levels during the diagnostic oral glucose tolerance test (OGTT). The values used to define this category were chosen to achieve a frequency of intermediate glucose equivalent to the frequency of overweight in the HAPO study cohort. BMI was measured at the time of the diagnostic OGTT and converted to equivalent WHO categories by regression analysis. Uweight, underweight; GDM, gestational diabetes mellitus; HAPO, hyperglycemia and adverse pregnancy outcome.

arm 30.2 ± 5.1 kg. Once again, in this study, women in the intervention arm had lower weight gain, there were lower rates of LGA and macrosomia in infants, and women had lower rates of preeclampsia.⁴⁷

In contrast, there is only one completed trial (the “LIMIT” study) that is sufficiently powered to examine maternal and perinatal outcomes after a lifestyle intervention in overweight

and obese women, and the results of this study were disappointing.⁴⁸ Essentially this study aimed to limit weight gain in overweight and obese pregnant women through lifestyle intervention. This study demonstrated that despite three face-to-face visits (including two visits with a research dietitian), three phone calls to assist in lifestyle modification, detailed individualized dietary advice, and a program tailored to stages of change theory, with detailed analysis of barriers to change, and individualized assistance, there was no difference in weight gain and no difference in any maternal or neonatal outcome (except for a reduction in infants weighing over 4 kg, although no difference in infants born LGA).

There have been numerous small randomized controlled trials of lifestyle and other interventions in overweight and obese women that have demonstrated reduced weight gain in pregnancy, and some have demonstrated reduced neonatal weight. However, other maternal and neonatal outcomes have not been examined. These studies have been summarized in meta-analyses.^{49,50} To date, the benefits seen in these small studies were not demonstrated in practical interventions that are affordable at a population level.⁴⁸

At present, it would appear that diagnosing and treating gestational diabetes in overweight and obese women has the best evidence with regard to limiting weight gain, preventing maternal adverse outcomes, and preventing neonatal adverse outcomes. However, it is important to note that the long-term impacts of any of these interventions on the health of adult offspring are as yet unproven and will need to be carefully examined.

Population risks and prevention

Another consideration in addressing obesity and GDM is their relative importance across the entire population of women undergoing pregnancy. A number of studies have attempted to address this issue. In this context, ascertainment bias

regarding glycemia in pregnancy and treatment confounding due to active intervention for GDM remain major issues.

A recent report by Black et al.⁵¹ regarding a cohort of 9835 women from Southern California with a high prevalence of overweight (32%) and obesity (28%) reported that, on a population basis, overweight and obesity accounted for 21.6% of LGA in women without and 23.3% in women with GDM. In their cohort, 75% of women who developed GDM were overweight or obese. This study also emphasized the importance of gestational weight gain as a determinant of LGA. These conclusions depend heavily on the background population, as in the global HAPO study cohort, the prevalences of overweight (22%) and obesity (14%) were much lower.⁵²

Similar findings have been noted in other studies. Kim et al. reported on a cohort from Florida.⁵³ Twenty percent of this cohort were obese and 24% overweight. These authors concluded that gestational weight gain was the major potentially modifiable factor in the prevention of LGA births. Alberico et al. reported on a cohort from Italy⁵⁴ and concluded that maternal obesity, GDM, and gestational weight gain all warranted careful assessment during pregnancy.

In summary, it is clear that, especially in populations with a high prevalence of overweight and obesity, these factors constitute a large fraction of the population risk of LGA. However, as noted previously, therapeutic strategies for addressing obesity in pregnancy have proved disappointing, in contrast to the positive results noted for the “glucocentric” treatment of GDM.

Evidence gaps and evidence: Practice gaps and future research

From the evidence presented earlier, it is clear that both GDM and maternal obesity are associated with a similar spectrum of adverse pregnancy outcomes, especially those related to

excessive fetal growth and adiposity and to hypertensive complications of pregnancy. GDM and obesity commonly, but not inevitably, coexist, and the development of common preventative and therapeutic strategies seems an attractive prospect.

Despite the epidemiologic data showing associations of GDM and obesity with adverse pregnancy outcomes, our understanding of the mechanisms underlying these associations remains limited. The Pedersen hypothesis has served as a useful framework for considering the pathogenesis of hyperglycemia in pregnancy,¹⁸ but even our most energetic approaches to achieving normoglycemia have not normalized pregnancy outcomes, particularly with the addition of obesity as a common comorbid condition. Specific therapy targeted a pregnancy dyslipidemia in GDM and obesity seems attractive in principle but difficult in practice due to safety concerns.¹⁵ The exploration of metabolic inflammation and its consequences in pregnancy may also improve our mechanistic understanding,^{18,24,55,56} but again the therapeutic options with current agents appear to be limited.

As previously noted, interventions commenced during pregnancy appear to have limited efficacy in preventing the complications of obesity. This aligns with the observation that, in obese women (in contrast to women of normal weight), prepregnancy weight is more closely associated with neonatal adiposity than weight gain during pregnancy.⁵⁷ Thus, preventative and therapeutic measures may need to be initiated preconception to reap positive benefits.

By contrast, the efficacy of therapy for GDM is well demonstrated. Effective implementation of GDM diagnostic and therapeutic strategies^{58–60} appears to have the greatest potential for proven benefit at the current time.

Future research should concentrate on delineation of the pathogenesis of obesity and GDM through basic and clinical studies; the development of effective strategies to target both conditions before, during, and after pregnancy; and the effective implementation of treatments that are known to be effective but are currently underutilized.

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31 Obesity versus glycemic control: Which contributes more to adverse pregnancy outcome?

Amir Aviram and Yariv Yogev

Introduction

Obesity has long been recognized as a global health concern, be it among adults, adolescents, or children, of both sexes. Over the past three decades, the prevalence of overweight and obese adults has more than doubled, with over a third of women aged 20 years and above being overweight and 14% obese.¹ According to the latest data from the Organization for Economic Cooperation and Development (OCED), more than half of the adult population in 20 out of 34 OECD countries are overweight or obese.² The World Health organization (WHO) and the National Institute for Health (NIH) define overweight as a body mass index (BMI) of 25–29.9 and obesity as a BMI of 30 or greater. Obesity is also subcategorized into three subgroups: class I (BMI of 30–34.9), class II (BMI of 35–39.9), and class III (BMI of 40 or greater).³

As obesity becomes an ever-growing concern, the number of women of reproductive age who are overweight or obese increases, and the incidence of obesity among pregnant women is now estimated between 18.5% and 38.3%.⁴ Maternal overweight is now a known risk factor that affects the vast continuum of pregnancy. Fertility and fecundity rates are lower among overweight and obese women, in spontaneous conception as well as in artificial reproductive techniques.⁴ During pregnancy, these women are more susceptible to pregnancy hypertensive disorders, gestational diabetes mellitus (GDM), respiratory complications, and thromboembolic events.^{4–6} Numerous studies have examined the impact of obesity on labor-related complications. As delivery approaches, overweight women have slower labor progression rate, higher rate of cesarean deliveries, and more surgery-related complications such as difficult spinal, epidural, or general anesthesia, wound infection, and endomyometritis.^{4–6} As for the fetus and neonate, complications include congenital malformations, large-for-gestational-age (LGA) infants, stillbirths, shoulder dystocia, and adolescent complications such as obesity and diabetes.^{4–6}

Weight gain, obesity, and pregnancy

The amount of weight gain recommended in pregnancy is controversial. Historically, obstetricians used to restrict weight gain to 15 lb, regardless of race, ethnicity, or prepregnancy weight. In the 1970s, a more lax approach to weight gain was followed, allowing weight gain for up to 20–27 lb. In 1990, the Institute of Medicine (IOM) published guidelines based on the effects of weight gain on fetal size. The new recommendations were based on prepregnancy BMI: weight gain of 28–40 lb for BMI of 19.8 and lower, 25–35 lb for BMI of 19.9–26, and 15–25 lb for BMI of 26.1 and greater. The IOM stated that the effect of weight gain on fetal size diminishes as the mother's prepregnancy BMI increases.⁷ This approach considered only immediate fetal outcomes and disregarded long-term maternal and neonatal effects. This concept was challenged in the past decades when studies evaluated the association between maternal weight gain, obesity, pregnancy outcome, and future development of diabetes in the mother and the child.

Rooney et al.⁸ evaluated a cohort of 540 women who had documented weight over a 5-year postpartum period. They concluded that excess weight gain and failure to lose weight after pregnancy are important and identifiable predictors of long-term obesity. Edwards⁹ reported that obese patients gained an average of 5 kg less during pregnancy and were more likely to lose weight or not gain weight at all compared with normal-weight women. Obese women who lost or did not gain any weight had lower mean birth weights and higher rates of small-for-gestational-age (SGA) infants in comparison to obese women who gained 1 lb (0.45 kg) or more. The incidence of macrosomic fetuses increased significantly only in the group that gained 12 kg or higher. No weight gain and weight gain up to 11.5 kg were associated with a macrosomia rate of 12.5%–13.3% compared with a background rate of 10% in nonobese women. Therefore, they recommend weight gains of 15–25 lb for obese women and 25–35 lb for normal-weight women to optimize fetal growth.

Bianco et al.¹⁰ reported that weight gain of more than 25 lb was strongly associated with birth of LGA infants. However, poor weight gain did not appear to increase the risk of low-birth-weight infants. Luke and associates reported that for every kilogram of gestational weight gained, birth weight increased by 44.9 g for underweight women, 22.9 g for normal-weight women, and 11.9 g for overweight women. For every kilogram of retained weight, birth weight was increased by 35.6 g for underweight women, 15.9 g for normal-weight women, and 5.1 g for overweight women.¹¹ These findings suggest that beyond a certain level of weight gain, there is an increase in birth weight at the expense of increasing maternal postpartum obesity for women who have gained an excessive amount of weight during pregnancy.

As the prevalence of obesity increased and evidences regarding adverse pregnancy outcomes in obese pregnant women accumulated, the IOM issued new guidelines for pregnancy weight gain in 2009, taking into account both maternal and fetal health.¹² The recommended weight gain for underweight women (BMI < 18.5) is 12.5–18 kg, for normal-weight women (BMI 18.5–24.9) 11.5–16 kg, for overweight women (BMI 25.0–29.9) 7–11.5 kg, and for obese women (BMI 30 and greater) 5–9 kg. Hull and colleagues examined whether differences exist in infant body composition based on the new IOM guidelines.¹³ It was found that infants of obese mothers had greater percent fat compared with infants of normal-weight and overweight mothers. Within the excessive weight gain group, infants of normal-weight mothers had less percent fat than infants of obese or overweight mothers. Another study by Vesco et al. found that obese women gaining weight above the IOM 2009 recommendations did not decrease the risk for SGA but increased the risk for delivering LGA or macrosomic infants, and that obese women gaining weight below the IOM recommendations had higher risk for delivering SGA and lower risk for LGA infants.¹⁴ Bodnar and associates demonstrated that the prevalence of excessive gestational weight gain (GWG) declined, and weight loss increased, as obesity became more severe.¹⁵ Generally, weight loss was associated with an elevated risk of SGA, medically indicated and spontaneous preterm delivery, and high weight gain tended to increase the risk of LGA and medically indicated preterm delivery.

Getahun and colleagues examined if BMI changes between two consecutive pregnancies are associated with increased risk for LGA in the second pregnancy.¹⁶ They found that women who were overweight or obese in both pregnancies had increased risk for LGA infant, and that any decrease in BMI attenuated the risk. They also concluded that 17.1% of LGA infants of underweight mothers, 13.2% of LGA infants of normal-weight mothers, and 7.6% of LGA infants of overweight mothers could be prevented if BMI had not increased between pregnancies.

Obesity and its late sequelae may prove to be one of the greatest threats to adult health in the developing world in this century.¹⁷ Different experiments on animals led to some interesting results. Howie et al.¹⁸ found that rats whose

mothers were fed with high fat diet during pregnancy and lactation, as well as others fed with high fat diet from weaning up through pregnancy, were hypoleptinemic and hypoinsulinemic at birth, compared with controls. As adults nourished with postweaning high fat diet, these rats were significantly more obese than controls and characterized with hyperinsulinemia and hyperleptinemia. It is of interest that a lifetime of high fat nutrition produced a phenotype similar to high fat nutrition restricted to pregnancy and lactation alone, thus suggesting that the postnatal sequelae of maternal high fat nutrition occurs independently of preconceptional diet. Laitinen and colleagues¹⁹ found that children of overweight or obese women had higher BMI at different ages until 31 years old than did children of normal- or underweight mothers. At the age of 31, measures of circumferences of the waist and hip and waist-to-hip ratio were higher in those born to mothers with higher BMI. Forsen et al.²⁰ showed that Finish men whose mothers had a high BMI in pregnancy had a 1.24 hazard ratio for coronary heart disease for every standard deviation increase in the mothers' BMI. In south India, glucose and insulin metabolism in 506 men and women aged 39–60 were tested. The researchers noticed that those with non-insulin-dependent diabetes mellitus were born to mothers who tended to be heavier than average during pregnancy.²¹

Obesity and gestational diabetes mellitus

The association of obesity and carbohydrate intolerance in pregnancy is well established. Bianco performed a retrospective study comparing 613 patients with BMI of >35 with more than 11,000 women with normal BMI, and found that the rates of type 2 diabetes and GDM were 4.5-fold and 3.3-fold higher, respectively, among the obese group.¹⁰ Kumari et al. examined pregnancy outcomes among women with BMIs of >40 and found a GDM rate of 24.5% versus 2.2% among normal BMI patients.²² In one of the largest studies concerning obesity in pregnancy, including more than 287,000 patients (of which approximately 79,000 are overweight patients and 31,000 are obese), the odds ratio (OR) for developing GDM was 1.68 for overweight patients and 3.6 for obese patients.²³ Weiss et al.²⁴ published the results of their 16,102 patients and demonstrated that a BMI of 30–34.9 was associated with an OR of 2.6 for developing GDM, and that a BMI of 35 and greater held an OR of 4.0 for GDM. Other studies of different cohort sizes supported these observations.^{25,26} Super obesity (BMI equal to or greater than 50) was found to be associated with a higher rate of GDM compared with normal-weight or other obesity classes' women.²⁷ A meta-analysis of 20 studies concluded that the OR for developing GDM are 2.15 (95% CI 1.82–2.53), 3.56 (3.05–4.21), and 8.56 (5.07–16.04) among overweight, obese, and severely obese gravidas, respectively.²⁸ Another study sought to evaluate the percentage of GDM attributable to overweight and obesity. The percentages of GDM attributable to BMI were calculated to be 15.4%, 9.7%,

and 21.1% for overweight, obese, and severely obese, respectively. The authors concluded that if all overweight and obese women had the same GDM risk as normal-weight women, nearly half of GDM cases would be prevented.²⁹

Apart from the well-established correlation between type 2 diabetes among nonpregnant women and obesity, attempts have been made to further elucidate the association between obesity and GDM. Colomiere and associates published their work about insulin signaling and glucose transporter expression in maternal skeletal muscle and subcutaneous adipose tissue. They found that both skeletal muscle and adipose tissue from obese women demonstrated lower GLUT-1 and GLUT-3 mRNA expression, leading them to conclude that this may be the cause of GDM.³⁰

Not until long ago, GDM was not proved to result in adverse pregnancy outcome. Only in 2005 did the pioneering work of Crowther and associates³¹ as well as Langer and associates³² demonstrated that the treatment of GDM reduces perinatal complications. Later, Landon et al. reiterate these results.³³ In fact, it was also shown that mild carbohydrate intolerance, in the absence of confirmed GDM, results in various adverse outcomes.^{34,35}

Since obesity is a substantial risk factor for GDM, and since GDM may lead to adverse pregnancy outcomes, a series of dilemmas arise: is there a difference between overweight or obese and normal-weight GDM patient, and if there is, are glycemic control goals of obese and overweight patients different from those of lean GDM patients and what treatment adjustments are needed for achieving those goals?

Several investigators sought the answer for the first question. Ben-Haroush et al. found that the prevalence of LGA neonates was higher in obese (BMI of ≥ 30) GDM patients compared with normal-weight GDM patients.³⁶ Another study compared four groups of patients: reference group (normal weight, no GDM), normal-weight GDM, obese GDM, and obese with no GDM. It was found that obese GDM patients had higher rates of cesarean deliveries, preeclampsia, macrosomia, and higher mean birth weights than lean GDM patients. Additionally, after accounting for confounders, obese GDM patients had a two- to threefold higher risk for macrosomia and cesarean deliveries, while the lean GDM patients had no such increased risk.³⁷ A subanalysis of the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study among more than 23,000 patients revealed similar results. The adjusted OR for LGA neonate, cesarean delivery, preeclampsia, and shoulder dystocia were calculated for the same four groups as depicted earlier. The results demonstrated an OR of 3.3 for LGA neonate among obese GDM (compared with 1.99 for lean GDM), an OR of 2.3 for cesarean delivery (compared with OR 1.5), an OR 5.3 for preeclampsia (compared with 1.7), and an OR of 1.7 for shoulder dystocia (compared with nonsignificant OR).³⁸ Furthermore, obesity was found to worsen maternal and perinatal outcome regardless of treatment modality.³⁹ It was suggested that one mechanism responsible for LGA neonates among obese GDM women is hypertriglyceridemia, despite glycemic control.⁴⁰

Glycemic control

The second question raised earlier was whether glycemic control goals of obese and overweight patients different from those of lean GDM patients and what treatment adjustments are needed for achieving those goals.

Early in 1987, Leikin and colleagues tried to solve this dilemma. They conducted a prospective study in which they divided GDM patients into two groups. The first group had fasting serum glucose levels of 95 mg/dL or less on oral glucose tolerance test and was treated with diet alone, and those with higher levels were treated with diet and insulin. The diet-treated group and lean GDM patients receiving insulin treatment had the same rate of macrosomia as the nondiabetic group. However, obese GDM patients treated with insulin demonstrated a higher rate of macrosomia.⁴¹

Another study aimed at answering this complex question was performed by Schaefer-Graf et al.⁴² They evaluated different parameters among GDM patients and found that while mean level of glycemic control was similar among mothers of macrosomic and nonmacrosomic neonates (except for fasting glucose levels at 32–35 weeks), macrosomia rates were higher among the obese patients. They concluded that the association between glycemic control and macrosomia was limited, while obesity appeared to be a strong risk factor for macrosomia throughout pregnancies with GDM. In their words, “in obese women, the high fetal macrosomia rate did not appear to be normalized by therapy based on maternal euglycemia.”

Yogev and associates sought to determine whether pregnancy outcomes differ between obese (BMI above 30 but less than 35) and morbidly obese (BMI of 35 or greater) GDM patients by analyzing retrospectively a cohort of 4830 patients with GDM. The rates of obesity and morbid obesity were 15.7% and 11.6%, respectively. Similar rates of cesarean section, fetal macrosomia, shoulder dystocia, composite outcome, and metabolic complications were noted. Of note, no differences were found in the rate of desired glycemic control, although a higher rate of insulin treatment was needed among the morbidly obese.⁴³ Another study by Joy examined the impact of obesity on pregnancy outcomes among GDM patients treated by diet, oral hypoglycemic agent, or insulin. Although glycemic control data were missing, in each group, obesity was associated with adverse outcome, suggesting its pivotal role.³⁹

Langer et al. performed a study comparing four groups of patients (diet treated with good glycemic control, diet treated with poor glycemic control, insulin treated with good glycemic control, and insulin treated with poor glycemic control) stratified by weight. It was found that obese and overweight GDM patients treated with insulin who achieved good glycemic control showed no increased risk of composite outcome, macrosomia, and LGA in comparison with normal-weight GDM patients.⁴⁴ In contrast, obese patients with good glycemic control achieved by diet still demonstrated higher risk for composite outcome, LGA, and macrosomia. Poorly controlled overweight and obese patients, regardless of treatment modality, had significantly higher rates of composite outcome, metabolic complications, macrosomia, and LGA. It may be

that although obesity, in and of itself, translates into potential adverse outcomes in pregnancy, GDM women treated with insulin and possibly oral antidiabetic drugs who achieve targeted levels of glycemic control will have pregnancy outcomes comparable to those of normal-weight women. The improved outcome in the insulin-treated overweight and obese women may be due to an unidentified effect of insulin itself on the fetus or the activation of other metabolic fuel pathways.

Most and Langer later published their results concerning the impact of maternal weight gain on fetal growth among GDM patients in relation to treatment modality, BMI, and glycemic control. Among obese or overweight diet-treated women, the rate of LGA was fourfold higher, compared with insulin-treated women.⁴⁵

Olmos and associates studied the impact of obesity and glycemic control on rates of macrosomia.⁴⁶ They defined glycemic control using mean blood glucose and HbA1c levels. They reported that the prevalence of macrosomia was 14.9% among their patients with good glycemic control versus 28.1% in those with lesser glycemic control. They also reported macrosomia rates of 10.4% in the normal-weight group compared with 24.6% in the overweight group, although both groups had similar glycemic control levels and GWG. Their conclusion was that good glycemic control was not sufficient to reduce macrosomia rates in the presence of overweight or obesity.

Potential management and intervention

In obese women, a modification of risk factors prior to or early in pregnancy is recommended. Regarding prepregnancy interventions aimed at reducing the risk for GDM, Villamor and Cnattingius found that compared with women whose BMI changed between -1.0 and 0.9 units, women who gained three or more units had increased risk of preeclampsia, gestational hypertension, GDM, cesarean delivery, stillbirth, and LGA birth.⁴⁷ The associations were linearly related to weight change and were also noted in women who had a healthy prepregnancy BMI in both pregnancies. Ehrlich and colleagues sought to estimate the association between interpregnancy change in BMI and the risk of GDM in a second pregnancy. They found that compared with women who had no change in BMI, those whose BMI increased had an increased risk of GDM. Conversely, those whose BMI decreased had lower risk of GDM only if they were overweight or obese during the first pregnancy and lost at least two BMI units.⁴⁸

Dell'Agnolo and colleagues⁴⁹ found that women who underwent bariatric surgery had less obesity-related comorbidities such as diabetes mellitus and hypertension. Their infants were more likely to be appropriate-for-gestational-age (AGA) and be born at term. A systematic review published by Maggard et al. included 75 articles, and concluded that less maternal complications occurred following bariatric surgery (such as GDM and preeclampsia), and that neonatal outcomes were better than in obese controls.⁵⁰

Intervention during pregnancy is also available. Harrison and colleagues randomized 228 women at risk of developing GDM to a four-session lifestyle program aimed at acquiring adequate GWG or controls. They found that by 28 weeks, GWG was significantly lower among women in the intervention group, and a trend was noticed toward less GDM.⁵¹ Another study examined the effect of gestational weight loss among overweight and obese women after the diagnosis of GDM was established. Gestational weight loss was associated with less macrosomia, NICU admissions, and cesarean deliveries, yet rates of SGA neonates and deliveries <34 weeks increased.⁵² A study of similar design demonstrated lower mean birth weight among overweight and class I obese women with gestational weight loss.⁵³ Park and associates found that overweight/obese GDM patients gaining less weight than recommended by the IOM 2009 guidelines had better neonatal outcomes and better glycemic control and lower rates of insulin treatment.⁵⁴

A randomized trial of weight-bearing exercise (versus no exercise) from 8 weeks of pregnancy in women who did not normally exercise resulted in significantly higher birth weights in offspring of women randomized to exercise.⁵⁵ In another study, exercise two times/week or less was associated with low birth weight (adjusted OR, 2.64 95% CI 1.29–5.39) relative to women who exercised three to four times/week after adjustment for potential confounders including social class.⁵⁶ Dye et al.⁵⁷ demonstrated that women who were obese at the time of conception but exercised regularly had lower rates of GDM. A meta-analysis published in 2011 concluded that prepregnancy physical activity yielded a pooled OR of 0.45 (95% CI 0.28–0.75) for developing GDM, and that exercise in early pregnancy was also protective (OR 0.76, 95% CI 0.70–0.83). Several studies showed that moderate exercise in pregnancy did not appear to be harmful and that there was no association with premature labor or poor Apgar scores, thus reassuring the safety of exercise during pregnancy.^{58,59}

Summary

In conclusion, obesity is a risk factor for adverse pregnancy outcomes, including GDM. The hazardous combination of overweight and obesity with GDM increases the risks involved with GDM or obesity alone. It seems that while glycemic control is of utmost importance in GDM, the role of obesity may be even more critical than previously believed. We may hypothesize that the presence of obesity or overweight in a GDM patient alters metabolic pathways, thus mandating tighter and stricter glycemic control. Therefore, the desired and adequate levels of glycemic control among overweight and obese patients need to be established. Nonetheless, the importance of insulin therapy may lie beyond merely achieving glycemic control, but in regulating these aberrant metabolic pathways among overweight and obese patients. Prepregnancy and early pregnancy interventions aimed at weight loss are efficacious in reducing overweight-, obesity-, and GDM-related complications.

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32 Pharmacological treatment for the obese gestational diabetes mellitus patient

Fiona C. Denison and Rebecca M. Reynolds

Pandemic of obesity, diabetes, and diabetes in pregnancy

The World Health Organization has described the rising prevalence of overweight (defined as body mass index [BMI] $> 25 \text{ kg/m}^2$) and obesity (BMI $> 30 \text{ kg/m}^2$) in developing and developed countries as a global pandemic.¹ Between 1980 and 2013, the proportion of women with a BMI of 25 kg/m^2 or more increased worldwide from 29.8% (29.3–30.2) to 38.0% (37.5–38.5), and in at least seven countries including Kuwait, Libya, Qatar, and Samoa, the estimated prevalence of obesity in women now exceeds 50%. In developed countries, although the prevalence is much lower, the overall pattern and rise in rates of overweight and obesity parallels that of developing countries.

The peak age prevalence of obesity in women in developed countries is at 60 years, which is beyond the natural reproductive age. However, although obesity rates in younger women are lower than in older women, they are also rising in women of reproductive age.² As a consequence, pregravid maternal obesity is now the most common comorbidity of pregnancy, with overweight and obesity affecting up to 40% and 20% of the antenatal population, respectively. Recent evidence suggests that the peak age prevalence of obesity has started to fall in developed countries.¹ This is likely to further increase the proportion of women of reproductive age who are overweight and obese.

In parallel with the obesity epidemic, there is also a diabetes pandemic with increasing numbers of obese pregnant women having preexisting diabetes (typically type 2 but also type 1) or being diagnosed with gestational diabetes mellitus (GDM) during pregnancy. A proportion of these women will have previously undiagnosed type 2 diabetes. Due to the lack of consensus in diagnostic and screening criteria for GDM during pregnancy, accurate estimates of risk and prevalence of GDM are difficult to define. However, a meta-analysis in 2007 demonstrated that compared to normal-weight pregnant women, the risk of GDM was 3.56 (3.05–4.21)-fold higher if the woman was obese and 8.56 (5.07–16.04)-fold higher if

she was severely obese (BMI $> 40 \text{ kg/m}^2$).^{3,4} Recent studies suggest that the association between maternal obesity and GDM may be even higher with a population-based record linkage study reporting adjusted odds ratios for developing GDM of 11.90 (7.54–18.79) and 67.40 (37.84–120.03) in obese and severely obese women, respectively.⁵

Obesity, diabetes, and rationale for treatment

Obese women are at increased risk of developing GDM because they are more likely to enter pregnancy with pre-existing insulin resistance. To maintain euglycemia in the third trimester, a 200%–250% increase in insulin synthesis is required to compensate for the 50% reduction in insulin sensitivity.^{6,7} In the obese, this physiological adaptation either fails to occur or is insufficient to compensate for the reduction in insulin sensitivity with resulting hyperglycemia.^{8,9}

Both maternal obesity and diabetes in pregnancy are associated with increased risk of adverse outcomes for both mother and fetus.^{5,10–12} For the mother, these include increased risk of pregnancy-induced hypertension, preeclampsia, medically indicated preterm delivery, and cesarean section. For the fetus, these range from increased risk of miscarriage, congenital anomaly, macrosomia, and shoulder dystocia through to neonatal death and stillbirth. In addition, both maternal obesity and diabetes are recognized to have long-term adverse health consequences for the child.

Although the underlying mechanisms linking maternal obesity with adverse outcome remain unclear, the Hyperglycemia and Adverse Pregnancy Outcomes study demonstrated that fasting hyperglycemia was correlated with increased risk of adverse outcomes including cesarean section and fetal macrosomia. This relationship exists even when blood glucose levels are within the normal range. Fasting blood glucose levels are higher throughout pregnancy in obese women than in normal-weight women,¹³

so it is likely that relative hyperglycemia may in part explain some of the excess in morbidity observed in obese pregnancies. However, it is likely that other factors in addition to hyperglycemia and insulin resistance such as micronutrient deficiency, hyperlipidemia, and inflammation play a role in the pathogenesis of morbidities in the obese.^{14,15} This is supported by studies that demonstrate the effects of maternal glycemia and obesity, which are independent and additive for outcomes including cesarean section and macrosomia.^{16,17} Thus, although there is a clear rationale for treating hyperglycemia and insulin resistance caused by GDM in the obese to improve outcome, a therapy or therapies that could also treat maternal obesity, for example, minimizing maternal weight gain and reducing inflammation, might have the best chance of optimizing pregnancy outcome.

Overview of management of GDM in the obese

Dietary modification with home blood glucose monitoring is the first-line management for GDM in obese pregnant woman. This is covered in depth in Chapter 17. The key principles are to maintain a healthy, balanced diet, for example, using the “eatwell plate” as per dietary recommendations for nonpregnant individuals with newly diagnosed diabetes, with particular emphasis on avoiding refined carbohydrates, sugars, and fats. For most individuals, adherence to these dietary recommendations will result in a calorie deficit. In pregnancy, there are no guidelines to suggest that weight loss is recommended/advisable during pregnancy.¹⁸ The best available advice for gestational weight gain in pregnancy is from the Institute of Medicine Guidelines, which advises a weight gain of 5–9 kg during pregnancy for all women with BMI > 30 kg/m².¹⁹ This advice has not been looked at in the context of dietary advice for GDM, but for most obese women it would seem that advice to maintain weight during pregnancy is not unsafe.

In many women, dietary modification achieves acceptable glycemic control and no further treatment is required. However, in women with GDM who remain hyperglycemic despite dietary modification, pharmacological therapy is the next stage in management. Subcutaneous insulin therapy has traditionally been regarded as the next stage in management, but with new evidence of safety and efficacy of oral hypoglycemic agents in pregnancy, these are increasingly being used as second-line treatment after failure of dietary modification. Insulin is then added as third-line therapy if oral hypoglycemic agents do not meet glycemic targets or are not tolerated.

Pharmacological treatment

Oral agents

Metformin

Mechanism of action Metformin is a synthetically derived biguanide.²⁰ After oral ingestion, it is rapidly absorbed and transported via the portal vein to the liver where it inhibits

glucose absorption and substrate availability for hepatic gluconeogenesis.²¹ Metformin is actively transported to hepatocytes via organic cation transporter 1. It inhibits the mitochondrial respiratory complex I leading to reduced ATP synthesis and activation of AMP-activated kinase. This results in a reduction of lipid synthesis, inhibition of gluconeogenesis, and a decrease in circulating insulin and glucose. Metformin also stimulates insulin-mediated glucose uptake by the skeletal muscle and liver.²¹ This, together with reduced gluconeogenesis in the liver, increases insulin sensitivity.

In obese nonpregnant women with type 2 diabetes, the apparent clearance and volume of distribution of metformin are influenced by the lean body weight. Markers of renal function such as age and serum creatinine also influence clearance and distribution.²² During pregnancy, metformin clearance increases with gestation due to enhanced renal elimination. To maintain a therapeutic effect, the metformin dose may therefore need to be increased by up to 20% in the third trimester.²³ Whether increased maternal BMI has an additional influence on clearance and volume of distribution of metformin during pregnancy is not known.

Safety of metformin in pregnancy Over the last 10 years in the United Kingdom, metformin has increasingly replaced insulin as the first-line pharmacological agent for the treatment of GDM if women fail to achieve glycemic control after dietary modification. This change in practice is in large part due to at least 10 clinical studies (5 randomized controlled trials, 2 prospective nonrandomized trials, and 3 retrospective studies) that have all demonstrated that metformin is safe in pregnancy and achieves comparable (or better) glycemic control compared to insulin or the sulfonylurea glibenclamide.^{24–32}

Metformin crosses the placenta, with umbilical cord concentrations at the time of delivery being at least half the maternal concentrations.^{23,33} In some cases, they exceed maternal concentrations. It is therefore important to follow up babies exposed to metformin in utero.

Short-term outcomes

Maternal outcomes Metformin is generally acceptable to women and well tolerated during pregnancy, with only 2%–7% of women being unable to take it due to its mainly gastrointestinal side effects. Other reported side effects are either very rare (lactic acidosis) or relatively minor (erythema in hypersensitive individuals). There is no evidence that maternal BMI affects the side effect profile of metformin during pregnancy.

Between 10% and 46% of women with GDM treated with metformin require insulin in addition to metformin to maintain euglycemia as pregnancy progresses.^{24,26,28,29,31} Higher maternal BMI and fasting blood glucose at diagnosis and early gestation at diagnosis of GDM are associated with increased need for supplemental insulin at an earlier gestation.^{27,28} Difference in the racial groups, time of blood glucose monitoring (pre- or postprandial), and the threshold for starting supplementary therapy (1 vs. 2 or 3 high home

blood glucose monitoring readings) may also explain the wide range in need for supplemental insulin between different trials. However, in those women who do require supplemental insulin, the dose of insulin required is consistently lower in women taking metformin and insulin as opposed to metformin alone. For example, in the Metformin versus Insulin for the Treatment of Gestational Diabetes (MiG) trial, participants on metformin required a significantly lower median dose of 42 U insulin, compared to the patients who received insulin therapy alone required a median dose of 50 U.²⁸

Excessive weight gain during pregnancy in obese women is associated with increased risk of complications including preterm birth, cesarean delivery, macrosomia, and childhood obesity.³⁴ Trials by Balani et al.,²⁴ Niromanesh et al.,³¹ and Rowan et al.²⁸ reported less gestational weight gain in women on metformin compared to other pharmacological agents. The underlying mechanism for this is not clear. In management of people with type 2 diabetes (who are not pregnant), metformin is regarded as being weight neutral and is not prescribed as a “weight loss” drug. In randomized controlled trials in women with polycystic ovarian syndrome (PCOS), with associated insulin resistance but not overt type 2 diabetes, treatment with metformin has not been associated with significant weight loss.²⁰ However, limiting gestational weight gain has potential health benefits for mother and offspring, particularly in the obese.

Fetal outcomes There is no evidence that metformin treatment is associated with increased risk of congenital anomalies. In the majority of trials, no difference was identified in frequency of large for gestational age, small for gestational age, macrosomia, birth weight, and neonatal unit admission.^{26–29,31,32} Metformin is also associated with lower risk of neonatal hypoglycemia compared to insulin.

The relationship between metformin use and preterm birth rates is less clear. In the MiG trial, the rates of spontaneous (5.0% vs. 3.5%) and iatrogenic (7.2% vs. 4.1%) preterm birth were higher in women treated with metformin ($n = 363$) compared to insulin ($n = 370$).²⁸ This reached significance when both spontaneous and iatrogenic preterm birth rates were combined (12.1% vs. 7.6%; metformin compared to insulin treated; $p < 0.04$). In contrast, there was no difference in spontaneous preterm birth rates ($p = 0.3$) between metformin ($n = 50$ recruited, one spontaneous delivery at 36 weeks gestation) and insulin ($n = 50$, three spontaneous deliveries at 31, 33, and 36 weeks therapy) in the Ijas trial,²⁷ and there was an increase in iatrogenic (15.0% vs. 7.6%) but not spontaneous (4.2% vs. 4.9%) preterm birth rates in the insulin-treated ($n = 399$) compared to metformin-treated ($n = 471$) group in the Goh trial ($p < 0.005$).²⁶ Maternal obesity is associated with increased risk of iatrogenic but not spontaneous preterm birth rates.⁵ Differences in maternal BMI between trial participants may therefore in part explain inconsistencies about whether metformin does or does not influence preterm birth rate.

Long-term outcomes

Maternal outcomes The impact of metformin treatment on maternal weight postpartum is less certain. A follow-up study of women with PCOS who were randomized to metformin (2000 mg daily) or placebo from first trimester to delivery reported maternal and offspring follow-up at 1 year. Despite the use of metformin being associated with less weight gain during pregnancy (3.2 ± 2.0 vs. 4.2 ± 4.3 kg, metformin compared to placebo; $p < 0.03$), women randomized to metformin lost less weight from the end of pregnancy to 1 year postpartum (-2.1 ± 3.6 vs. -4.1 ± 4.9 kg; $p < 0.03$) and had higher BMIs (30.6 ± 8.1 vs. 27.6 ± 6.1 kg/m²; $p < 0.004$) compared to those in the placebo group.³⁵ This is despite there being no difference in maternal BMI between metformin and placebo groups during the first trimester at randomization (32.7 ± 6.9 vs. 32.0 ± 7.3 kg/m², metformin compared to placebo; $p = 0.51$). To date, there are no data on postpartum weight and BMI in the obese GDM managed with metformin during pregnancy.

Offspring outcomes Maternal obesity is associated with increased risk of offspring obesity due in part to fat preferentially being stored in visceral as opposed to subcutaneous depots.³⁶

The MiG trial has followed up children at 2 years post-delivery.^{28,37} Compared to the insulin group, the children exposed to metformin in utero had larger subscapular and biceps skinfolds and greater upper arm circumferences. There was no difference in total percentage body fat, fat mass, or central fat measures between the two groups. The investigators concluded that in utero exposure to metformin may predispose children to laying down fat stores in healthier subcutaneous fat depots, thus reducing the risk of developing insulin resistance and obesity in later life. Others have subsequently cautioned against overinterpreting the results due to the crude indirect measures used to measure visceral fat depots, small numbers at follow-up, and investigators not being blinded to the treatment group of the mother.³⁸

If alterations in offspring body composition do exist following in utero exposure to metformin, whether these persist into childhood is not certain. Albeit in a different patient cohort, Ro et al. reported follow-up of a randomized controlled trial on women with PCOS randomized to metformin or placebo in pregnancy.³⁹ At 8 years, there were no differences in offspring body composition, weight, or height between those exposed to metformin and those exposed to placebo. Children exposed to metformin in utero did however have a higher fasting glucose level (4.93 vs. 4.60 mmol/L, $p = 0.04$) and a trend toward a lower LDL cholesterol level (2.42 vs. 2.99 mmol/L, $p = 0.07$) and higher systolic blood pressure (106 vs. 101 mmHg, $p = 0.05$).

Although the follow-up studies are reassuring about the safety of metformin during pregnancy, caution should be exercised about concluding that its use in the obese GDM will reduce the risk of the offspring in developing insulin resistance in later life due to redistribution of fat depots. Further long-term follow-up studies are needed.

Glibenclamide

Mechanism of action Glibenclamide is a second-generation sulfonylurea, an insulin secretagogue. It binds to pancreatic β -cell ATP calcium channel receptors and stimulates release of insulin from the functional cell mass of the pancreas. It also increases insulin sensitivity in peripheral tissues.^{40,41} Glibenclamide is therefore an effective treatment for the inadequate insulin secretion and insulin resistance that occur in the obese GDM.

Glibenclamide is well absorbed following oral administration. It reaches peak concentration in approximately 3 hours, and following metabolism in the liver, it has a half-life of 8 hours. Glibenclamide is cleared more rapidly in pregnancy due to its being metabolized by the cytochrome P450 enzymes, the activity of two (CYP2C9 and CYP3A) being increased in pregnancy. In nonpregnant women with type 2 diabetes, studies demonstrate that obesity has no effect on glibenclamide pharmacokinetics and pharmacodynamics.⁴² There are no studies that have investigated whether obesity affects glibenclamide pharmacokinetics and pharmacodynamics during pregnancy.

Safety of glibenclamide in pregnancy Glibenclamide was the first oral agent to be tested in clinical trials to manage GDM in pregnancy.⁴³ It has subsequently been trialed in a large number of randomized controlled trials, nonrandomized trials, and retrospective studies.^{44–54} To date, most trials demonstrate that glibenclamide is effective in most women in optimizing glycemic control.

Initial clinical trials⁴³ suggested that fetal exposure to glibenclamide was minimal because levels were undetectable in cord blood.⁵⁵ However, more recent studies demonstrate that glibenclamide crosses the placental barrier with a cord-to-maternal plasma concentration ratio of 0.7.⁵⁶ Although glibenclamide is metabolized by the fetus and the placenta actively pumping glibenclamide from the fetus to the mother via the ABC transporters, fetal drug concentrations reflect maternal serum levels.⁵⁷

Short-term outcomes

Maternal outcomes Glibenclamide is generally well tolerated by women during pregnancy. Hypoglycemia and weight gain are the most common side effects reported by individuals taking glibenclamide who are not pregnant. Therefore, women who are started on glibenclamide treatment will need to be advised about symptoms and management of hypoglycemia and to take the medication with food. Weight gain is a well-recognized side effect of glibenclamide due to stimulation of insulin secretion with consequent enhanced glucose absorption and storage in adipose tissue, but there are no data on whether the use of glibenclamide in GDM has a significant impact on gestational weight gain. Although side effects such as skin itching, rashes, mild nausea, and heartburn are relatively common, these usually settle if treatment persists. Other side effects such as elevated liver enzymes are less common, and it only rarely causes jaundice.

Between 16% and 21% of women with GDM treated with glibenclamide require insulin in addition to glibenclamide to

maintain euglycemia as pregnancy progresses.^{50–54} Although the presence of maternal obesity *per se* does not predict treatment failure, factors such as early diagnosis and treatment of gestational diabetes, baseline hyperglycemia, increased maternal age, and parity, which are more prevalent in the obese, do predict increased risk of failure.^{50–54} In nonpregnancy, glibenclamide is associated with moderate weight gain, and gestational weight gain in women treated with glibenclamide is comparable to women with GDM treated with insulin.

There are conflicting data about whether compared to insulin therapy glibenclamide is associated with no change or increased risk of preeclampsia.⁵⁸ In a retrospective study by Jacobson et al.,⁵⁸ outcomes were compared in women treated with insulin ($n = 268$) and with glibenclamide ($n = 236$). Women treated with glibenclamide were more than twice as likely to develop preeclampsia (odds ratio [OR] 2.32; 95% confidence interval [CI] 1.17–4.63) compared to those managed with insulin. In contrast, in a smaller study ($n = 78$ treated with insulin; $n = 44$ treated with glibenclamide), there was no significant differences in the risk of preeclampsia between treatment groups.⁵⁹ Maternal obesity is associated with increased risk of developing preeclampsia⁵; thus until there is more conclusive trial evidence, it may be sensible to use alternative pharmacological agents in the obese mother with GDM with other risk factors for developing preeclampsia such as essential hypertension.

Fetal outcomes There is no evidence that glibenclamide is associated with increased risk of fetal anomaly. In the randomized controlled trial by Langer et al., in which women were randomized to receive glibenclamide or metformin, the trial was powered on the primary outcome of “desired level of glycemic control” and not less common neonatal outcomes.⁴³ The largest retrospective observational study compared outcomes in women with GDM treated with insulin ($n = 8609$, 80.6%) with oral hypoglycemic agents ($n = 2073$, 19.4% or which 99% were receiving glibenclamide).⁴⁹ After controlling for confounders including maternal weight, ethnicity, parity, and gestation at diagnosis, oral therapy was associated with increased risk of admission to the neonatal unit (OR [95% CI], 1.46 [1.07–2.00]), macrosomia (OR [95% CI], 1.29 [1.03–1.64]), and, if GDM was diagnosed early in pregnancy, stillbirth (OR [95% CI], 4.68 [1.02–21.5]). A small randomized controlled trial in women with GDM randomized to insulin ($n = 50$) and glibenclamide ($n = 49$) has demonstrated a 4.9% increased rate of intrauterine growth restriction ($p < 0.01$). Maternal obesity is independently associated with increased risk of neonatal unit admission, macrosomia, intrauterine growth restriction, and stillbirth.⁵ Whether maternal obesity contributes to increased risk associated with glibenclamide needs to be evaluated in future substantive trials.

Long-term outcomes

Maternal and offspring outcomes To date, there are no studies that report long-term maternal and offspring outcomes following glibenclamide use for GDM in either women of normal weight or obese.

Insulin

Subcutaneous insulin therapy is recognized as the standard for the treatment of GDM to achieve euglycemia after failure of dietary therapy in order to avoid the short- and long-term complications of poorly controlled glucose during pregnancy. A recent systematic review and meta-analysis of randomized controlled trials comparing therapeutic intervention for GDM with standard antenatal care included data from 10 studies including 3881 patients.⁶⁰ In these studies, interventions used in the experimental group were dietary modification and glucose monitoring, and insulin was administered if glycemic targets were not met with dietary modification. Treatment for GDM significantly reduced the risk for macrosomia (relative risk [RR], 0.47; 95% CI, 0.38–0.57), large-for-gestational-age births (RR, 0.55; 95% CI, 0.45–0.67), shoulder dystocia (RR, 0.42; 95% CI, 0.23–0.77), and gestational hypertension (RR, 0.68; 95% CI, 0.53–0.87) without causing any significant increase in the risk for small-for-gestational-age babies. No significant difference was observed between the two groups regarding perinatal/neonatal mortality, neonatal hypoglycemia, birth trauma, preterm births, preeclampsia, cesarean section, and labor induction. The heterogeneity of studies, for example, differences in study population, glycemic targets, and insulin regimens, does make comparison of studies challenging. Nevertheless, it is accepted that subcutaneous insulin therapy is effective at lowering blood glucose in women with GDM and that this is associated with improved outcomes for mother and baby.

With changes in clinical practice over the last decade in the United Kingdom, insulin is increasingly used as a third-line agent to supplement metformin therapy when metformin alone fails to control glucose levels or if metformin is not tolerated. Indeed in a survey of maternity units in Scotland in 2013, there was almost a universal use of insulin as a third-line agent (Stirrat, personal communication). Details of types of insulin preparation and typical insulin regimens for managing diabetes in pregnancy are described in detail elsewhere (Chapter 22). As in standard diabetes management, diabetologists will tailor an individual's insulin regimen and preparation after consideration of the woman's daily blood glucose profile and lifestyle. Thus women may require prandial quick-acting insulin and/or basal (long-acting) insulin or a basal-bolus regimen depending on the situation, and insulin requirements are likely to change during pregnancy. The 2013 Scottish survey highlighted that a range of different insulin preparations and regimens was used, including the use of fixed mixtures of insulin (Stirrat, personal communication). Women with GDM who need to start insulin therapy will require more intensive management during pregnancy, seeing a diabetes specialist nurse and diabetes consultant for education about insulin administration and dose titration as well as advice about management of hypoglycemia. There is no evidence that obese women with GDM should use a different injection site for insulin administration than is advised in a nonpregnant individual. If very large doses of insulin are required to control blood glucose, this may be associated with pain

at the injection site and/or need to inject more than once (most insulin pens have a maximum of 80 units), which may be cumbersome for the woman and lead to poor compliance, as observed in nonpregnancy.⁶¹ However, this would be unusual, even in an obese woman with GDM.

Increased prepregnancy BMI is a recognized risk factor for the need for insulin treatment of GDM. For example, in one study, prepregnancy BMI > 30 kg/m² was independently associated with the need for insulin treatment with an odd ratio of 2.35 (1.33–4.13).⁶² In this study, women with GDM were not offered oral hypoglycemic agents after failure of dietary therapy alone, and future studies will inform whether use of these agents is associated with decreased need for insulin in the obese mother with GDM.

What are the disadvantages for women of insulin therapy?

Given that insulin therapy has been regarded as the standard therapy and there is a wealth of data and experience of its use in women with type 1 and type 2 diabetes, why would women with GDM not want to be treated with insulin during pregnancy? Insulin has several disadvantages for women, often requiring multiple daily injections and with the recognized risks of hypoglycemia and weight gain. Many women fear injecting themselves with insulin, and in comparative trials, women prefer taking oral agents to insulin therapy.²⁸ Having a diagnosis of GDM has been shown to increase a woman's anxiety and result in a less positive pregnancy experience than in women without GDM.⁶³ Treatment with insulin appears to have further detrimental effects on maternal well-being in pregnancy. A recent survey of 1372 Australian women including 393 who reported their experiences of having GDM found that women taking insulin were significantly more likely to experience shock, fear, or anxiety.⁶⁴ This study highlights the need for healthcare professionals to provide additional support to these women when their treatment for GDM is intensified.

The increased insulin resistance associated with obesity in pregnancy may mean that insulin requirements are greater for obese women with GDM than for women of normal weight. These larger doses of insulin may increase the risk of excess gestational weight gain due to the anabolic actions of insulin described earlier. Women with GDM who are commenced on insulin treatment should therefore have additional dietetic input to minimize insulin-associated weight gain. Likewise, it is also important that obese women with GDM are advised to avoid excessive gestational weight gain as weight gain in the nonpregnant obese individual is associated with further increased insulin requirements.⁶⁵ If these observations are extrapolated to pregnancy, excessive gestational weight gain could lead to increased insulin requirements and a consequent vicious cycle of increasing insulin doses and increasing weight gain. Use of metformin in combination with insulin is associated with a lower total daily requirement of insulin,²⁸ and the combination of the weight-neutral effect of metformin and the lower insulin requirements may be beneficial in limiting gestational weight gain in the obese woman with GDM. However, further studies are needed.

Summary

In summary, it is highly likely that levels of maternal obesity and GDM will continue to rise in antenatal populations. As treatment escalates from dietary to oral agents through to polypharmacy with insulin, the level of intervention and the frequency of monitoring increase. At a national and international level, this is having a huge impact on the design and delivery of antenatal services with current models of antenatal care increasingly being unsustainable. It is therefore likely

that alternative methods of delivering effective care will be needed. Current developments include evaluating the use of telemetry as an alternative method of monitoring glycemic control in GDM reducing the need for hospital attendance and early-stage trials exploring combination therapy with metformin and glibenclamide as opposed to adding insulin as third-line management. The results of these studies and others are likely to fundamentally alter the management of GDM. This will have a particular impact on the obese due to the high prevalence of GDM in this antenatal population.

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33 Role of exercise in reducing the risks of gestational diabetes mellitus in obese women

Raul Artal

Introduction

The World Health Organization has identified a worldwide epidemic of obesity and diabetes and designated them as leading causes for premature mortality.¹ These conditions stem primarily from the sedentary lifestyle adopted by the contemporary society. Obesity is recognized as a chronic relapsing disease and is also a major cause for the diabetes epidemics. The benefits of adopting a healthy lifestyle in nonpregnant women, which includes weight reduction and physical activity, to prevent or manage diabetes has been well established in large clinical trials in the United States, China, and Finland.^{2–4}

Pregnancy and gestational weight gain have been a major contributor to the obesity epidemic in part because of the past practice and reluctance to prescribe lifestyle modification regimens to pregnant women. After pregnancy, 16.1% of nulliparous and 19.3% of parous women become obese.⁵ Many countries, among them the United States, have experienced a sharp rise in the incidence of gestational diabetes, of whom 60% will develop type 2 diabetes mellitus within 4 years.⁶ Women who are active prior to pregnancy and throughout pregnancy have the lowest prevalence of gestational diabetes.^{7–9}

Women with a BMI of 30–35 have an adjusted odds ratio (OR) of 2.6, and women with BMI greater than 35 have an adjusted OR of 4.0 for gestational diabetes compared with women with a BMI of less than 30.¹⁰

A multitude of maternal and fetal comorbidities have been linked to maternal obesity, gestational diabetes, and type 2 diabetes.¹¹

Historically, pregnant diabetic women were precluded from engaging in physical activities; to the contrary, they were prescribed prolonged periods of hospitalization or home bed rest.¹² The reluctance of prescribing lifestyle interventions to pregnant women stemmed primarily from the fear of potentially causing harm to the fetus. With the advent of sophisticated imaging and fetal monitoring over the past

decades, this concern has significantly diminished; however, prescription of lifestyle interventions that include judicious gestation weight gain and physical activity for pregnant women are not yet widely accepted or prescribed.

The 2009 Institute of Medicine (IOM) recommendations for gestational weight gain¹³ for overweight and obese women not only are counterintuitive^{14,15} but could also further amplify the risk of developing gestational diabetes, since pregnancy is a diabetogenic state characterized by progressive increase in insulin resistance, which worsens with additional weight gain. Recent studies that aimed at evaluating gestational weight gain below the IOM recommendations have reported no adverse effects, no restricted fetal growth (one of the IOM concerns) and better outcomes.^{15–17}

A strong association between higher BMIs, maternal plasma glucose levels, and pregnancy complications has been demonstrated by the Hyperglycemia and Pregnancy Adverse Outcome study.¹¹

The American Diabetes Association (ADA) in its *Standards of Medical Care in Diabetes—2014* recommends that among nonpregnant individuals at high risk for developing diabetes, structured programs that emphasize lifestyle changes that include moderate weight loss (7% of body weight) and regular physical activity (150 minutes/week) with dietary strategies including reduced calories and reduced intake of dietary fat should be prescribed.¹⁸ Over the past years, information has been accumulated to safely prescribe similar regimens of judicious weight gain and physical activities to pregnant women at risk for diabetes or those that are affected by either gestational diabetes or type 2 diabetes.^{16,17,19–23}

The American Congress of Obstetricians and Gynecologists (ACOG) in its guidelines for exercise during pregnancy and postpartum recommends to obese pregnant women to engage in healthy lifestyle modification that includes physical activities and judicious diets. ACOG supports the recommendation that a moderate exercise program should be part of the prevention and/or treatment plan for women with

gestational diabetes mellitus.^{24,30} ACOG also recommends that “for an obese pregnant woman who is gaining less weight than recommended but has an appropriately growing fetus, no evidence exists that encouraging increased weight gain to conform with the 2009 IOM guidelines will improve maternal or fetal outcomes.”²⁵

In 1985, the concept of lifestyle modification was introduced for the management of pregnant diabetics with a study comparing hormonal responses to light exercise of diabetic and nondiabetic pregnant women, and it was suggested that physical activity could be considered a safe intervention in pregnancy as well to improve and control glycemia.²⁶

Over the subsequent years, different investigators have confirmed and proposed various lifestyle intervention management schemes to prevent or manage gestational diabetes and type 2 diabetes prior to and during pregnancy.^{27,28} The ADA in its *Executive Summary: Standards of Medical Care in Diabetes—2014*¹⁸ states that “Women with a history of GDM found to have prediabetes should receive lifestyle intervention or metformin to prevent diabetes.” The American College of Sports Medicine (ACSM) and the ADA issued a joint statement in 2010: “Epidemiological studies suggest that higher levels of physical activity may reduce risk of developing gestational diabetes mellitus prior and during pregnancy.” Randomized clinical trials suggest that moderate exercise may lower maternal blood glucose levels in gestational diabetes mellitus.²⁹ The Royal College of Obstetricians and Gynaecologists and the Canadian Diabetes Association (CDA) consider exercise an adjunctive therapy for women with gestational diabetes.^{31,32}

The CDA guidelines also specify that the frequency, intensity, type, and duration of activity should be based on each individual’s obstetric risk.³²

Pathophysiology

The physiological and endocrinological changes in pregnancy are significant; pregnancy is considered to be a diabetogenic state and characterized by progressive insulin resistance, similar to the insulin resistance observed in patients with type 2 diabetes.^{24,33,34}

In overweight and obese patients, insulin resistance is by and large a result of the progressive increase in adiposity and hyperglycemia; increased fat storage will further increase the insulin resistance. During pregnancy, a major contributor to insulin resistance is the accumulating adipose tissue, which acts as an active organ, and placental and other hormones such as human placental lactogen, cortisol, progesterone, estrogen, tumor necrosis factor alpha, adiponectin, interleukin-6, resistin, and plasminogen activator inhibitor. Excessive weight gain in pregnancy and the increased adiposity lead to further increased release of adipokines and leptin that increase the oxidative stress that contributes to the insulin resistance.^{35,36} Exercise can reverse or prevent this process by stimulating muscle and liver glucose uptake and nonoxidatively metabolizing glucose into glycogen.^{37,38}

The glycogen repletion from the muscles and liver increases the insulin action that persists after exercise. Adiponectin regulates insulin sensitivity and glucose homeostasis, and low levels of adiponectin are associated with beta cell dysfunction.³⁹ Muscle binding of adiponectin translocates a glucose transporter type 4 (GLUT4)—which is an insulin-regulated protein found in adipose and striated muscle tissue and is responsible for the glucose transport into cells. Exercise increases glucose uptake by GLUT4 translocation, increasing the amount of aerobic enzymes in the skeletal muscles by as much as 20-fold upregulating lipid oxidation and mitochondrial biogenesis.

Exercise thus improves glycemia primarily through two mechanisms: (1) insulin-stimulated muscle glucose uptake and (2) insulin-independent glucose transportation (GLUT4). As such exercise reduces the hepatic glucose production and glycogen metabolism and also lowers total cholesterol and triglyceride while raising high-density lipoprotein levels.

Leptin has a key role in regulating energy intake and energy expenditure; during pregnancy, its level increases by 150%–200% in the second and third trimester over levels in the first trimester and twofold to threefold above nonpregnant levels.⁴⁰ In leptin-deficient subjects with lipodystrophy, decreased production of leptin by adipose tissue has been considered to be a cause for insulin resistance⁴¹; conversely, exercise-induced reductions in leptins have been ascribed to changes in energy balance, improvements in insulin sensitivity, and lipid metabolism.⁴²

Insulin sensitivity progressively decreases in pregnancy, and to counteract this process and maintain euglycemia during the third trimester in healthy pregnant women, insulin secretion increases two to four times.⁴³

The acquired decrease in insulin sensitivity particularly in obese women in pregnancy is the physiological background and rationale for recommending exercise as a logical intervention to either prevent or manage gestational diabetes and prevent further progression to diabetes during or after pregnancy.

While prescribing exercise in pregnancy, the anatomical and physiological changes associated with pregnancy have to be considered.³⁴

Exercise prescription for sedentary overweight or obese women to prevent or manage gestational diabetes

The basic components of exercise prescription include frequency, intensity, duration, and type.

Energy expenditure and thus insulin sensitivity depend on the frequency and amount of work (exercise) intensity and duration. As to type, aerobic exercise is most frequently prescribed to pregnant women, while experience with resistance exercise in pregnancy is more limited. Some of the studies conducted in pregnancy to prevent or manage gestational diabetes mellitus meet the requirements set for lifestyle modification by the ADA for nonpregnant, while other studies appear to not have met the ADA recommendation

or quantified the interventions with objective physiological measures to assess the efficacy of the interventions, or the training effect for energy expenditure, or measured the aerobic capacity at regular intervals to evaluate the level of training and efficacy, of the intervention (Table 33.2).

It is important to emphasize that bouts of exercise also play an important role in upregulating insulin sensitivity.⁴⁴ In our experience, 15 minutes of low-intensity frequent bouts of exercise do not result in significant changes in blood glucose levels in normal nondiabetic pregnant subjects⁴⁵ but do make a difference and improve glycemia in sedentary patients with gestational diabetes, particularly obese subjects.⁴⁶ It is important to note that in healthy normal pregnant subjects, continuous prolonged exercise in pregnancy at about 55% VO_2 or higher could significantly decrease glucose levels and result in hypoglycemia after 45–60 minutes of continuous exercise. Comparison has been studied for the same subjects during and after pregnancy⁴⁷ (Figure 33.1). Thus, continuous strenuous exercise beyond 45–60 minutes in pregnancy requires some form of supervision.

In the prospective nurses' health study, it has been demonstrated that prior to pregnancy, it is necessary to expend at least 1700 kcal/week (the equivalent of 16 hours/week) in light exercise or at least 840 kcal/week (the equivalent of 8 hours/week) in vigorous exercise to reduce the risk of developing gestational diabetes (Figure 33.2).⁴⁸

The nurses' health study has determined that the relative risk of gestational diabetes mellitus (GDM) was reduced by 17% with prepregnancy light exercise and 30% with more vigorous exercise.⁴⁸ In another study, it has been demonstrated that the exercise-induced changes with a homeostasis model assessment (HOMA) of insulin resistance, measured the following day postexercise, were negatively and curvilinearly correlated to energy expenditure (Figure 33.2).

The HOMA score is a measure of insulin resistance decreased by 30% in subjects who expended more than 900 kcal (strenuous) during one bout of exercise.⁴⁹ Similar

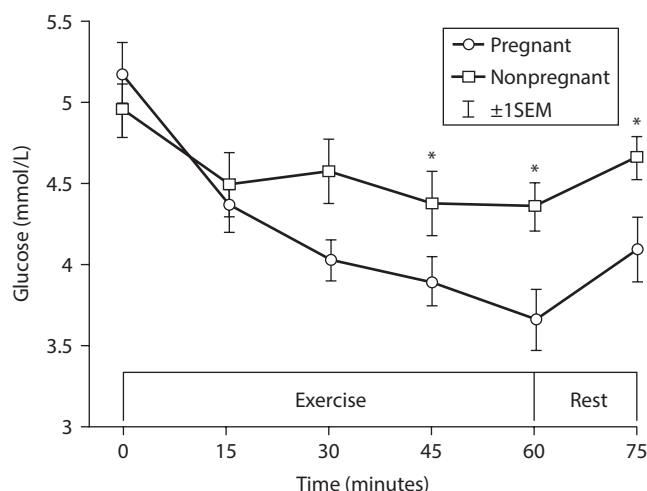


Figure 33.1 Glucose concentrations during prolonged exercise: Pregnant versus nonpregnant. * $p < 0.05$. (From Soultanakis, H.N. et al., *Semin. Perinatol.*, 20(4), 315, 1996. With permission.)

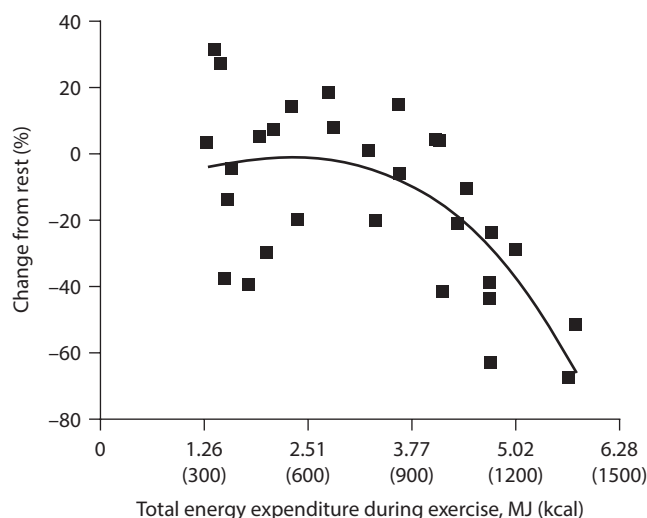


Figure 33.2 Energy expenditure during exercise. (From Magkos, F. et al., *Clin. Sci.*, 114, 59, 2008. With permission.)

results can be obtained in pregnancy through several bouts of exercise per week as has been illustrated in our own studies²⁷ (Table 33.1).

In terms of intensity, in a joint ACSM and American Heart Association exercise recommendations, light physical activity is defined as requiring less than 3 METs, moderate activities 3–6 METs, and strenuous activities greater than 6 METs.⁵⁵

METs or metabolic equivalents are used to quantify the metabolic cost of exercise in terms of oxygen consumption. The equivalent of 3.5 mL $\text{O}_2/\text{kg}/\text{minute}$ is 1 MET and is obtained at rest. Walking at a moderate pace for 1.5 miles/day will expend approximately 6 METs. Walking is the type of activity that can be readily prescribed and accepted by sedentary, overweight, or obese subjects.

Relevant to exercise prescription for pregnant diabetic patients and based on the aforementioned studies, we have established that pregnant women could safely complete at least one moderate bout of exercise of 30–45 minutes/day and if possible one bout of exercise after each meal to expend at least 200 kcal or more per day or approximately 6 METs/day and 1400 kcal/week, the necessary energy expenditure to obtain or maintain euglycemia in pregnancy. Less than 16 MET hour/week would not suffice to either prevent GDM or manage hyperglycemia of patients who have developed GDM A₂ or have preexisting diabetes. In our experience, within 10 days of initiating an exercise program in GDM patients, 60% will attain euglycemia.^{21,27,46} Physical activity in early and throughout pregnancy can prevent or reduce GDM risk.

Meeting the ADA criteria for the prevention or management of type 2 diabetes in nonpregnant subjects with impaired glucose tolerance, impaired fasting glucose, or A1C 5.7%–6.4% in our and other investigators' experience has been validated in pregnancy as well (Table 33.2). The combination of nutritional control and exercise has been demonstrated to better control glycemia also in pregnancy.^{27,28} It also appears that meeting the criteria

Table 33.1 Lifestyle intervention of diet and exercise for obese GDM patients study 1 (2007)

Characteristic	Subjects who lost weight or no weight change (n = 30)			Subjects who gained weight (n = 66)		
	Mean (SD)	n	%	Mean (SD)	n	%
Birth weight (g)	3286 (399)			3340 (612)		
Normal		23	96		43	77
LGA (>4000 g)		1	4		10*	18*
SGA (<2500 g)		0	0.0		3	5
GA (week)	39 (1)			38 (2)		
C-section		10	42		28	49
Vaginal		14	58		29	51
Exercise and diet		18	60		21	32*
Diet only		12	40		45	68*

Source: Reproduced from Artal, R. et al., *Appl. Physiol. Nutr. Metab.*, 32(3), 596, 2007. With permission.

* $p < 0.05$ compared to lost weight/no weight change.

established by the ADA for nonpregnant individuals to reduce the risk for or manage diabetes may be valid for pregnant subjects as well. This is illustrated in some but not all of the published trials in pregnant patients (Table 33.2). Clearly in many of these intervention trials in pregnancy, the subjects did not engage in activities sufficient to elicit normoglycemia.²² It also appears that in many of the interventional studies, the subjects' BMIs were by and large at or below 25–30. Significant is the fact that among subjects that engaged in even a minimum amount of exercise, certain comorbidities were precluded among them, fetal macrosomia and reduced cesarean sections.

A potential cause for intervention failure in many of the trials could be related to additional gestational weight gain. In our recent experience in the care of obese pregnant women with a BMI exceeding 30, a gestational weight gain of less than 5 kg for the duration of pregnancy has favorable outcomes.¹⁵

In a population-based birth cohort study conducted in Central New York, we compared GDM prevalence among pregnant subjects who engaged in physical activities to pregnant subjects who did not. Physical activity was associated with a 50% reduction in the rates of GDM among women with a BMI greater than 33 kg/m² (OR = 1.9, 95%, confidence interval 1.2–3.1) (see Figure 33.3).

This study suggests that exercise has a stronger and more immediate protective effect in women with higher BMI and that lifestyle interventions may be more effective and reduce insulin resistance and improve insulin sensitivity in subjects who are obese and insulin resistant than in those who are obese but metabolically healthy; this distinction remains to be studied. Since the data obtained for this study were obtained from birth certificates, we could not determine the timing, intensity, and duration of exercise and if the activities were conducted throughout pregnancy.⁸

Exercise prescription for sedentary, overweight and obese subjects

Over the years, we have developed exercise prescription regimens for sedentary, overweight, or obese women who are at risk for or acquired gestational diabetes or affected by type 2 diabetes.²⁷ Table 33.3 illustrates our current recommendations.

Summary and conclusions

Pregnancy poses a risk for pregnant women particularly overweight, obese, or sedentary women to develop gestational diabetes. Women that engage in any recreational physical activity during the first 20 weeks of pregnancy experience a 48% reduction in developing gestational diabetes when compared to sedentary women.^{8,57}

Several organizations based their recommendations on reviews and meta-analyses of randomized and nonrandomized clinical trials⁵⁸ have reached the conclusion that antenatal lifestyle interventions of judicious gestational weight gain and exercise could reduce or prevent gestational diabetes in the overweight and obese pregnant women and could be safely prescribed to pregnant patients who have acquired gestational diabetes or type 2 diabetes.

Pregnancy provides a unique opportunity to adopt lifestyle modification, since pregnant women have better access to medical care and supervision than any other time.

Practice points

- Obesity is currently the leading cause for gestational diabetes.
- Additional gestation weight gain in obese pregnant women increases the risk for gestational diabetes.

Table 33.2 Lifestyle interventions for overweight women

Author	Study	n	BMI	GWG (kg) ^b	ADA criteria	LGA ^a	Comment
1. Artal (2007) ²¹	Intervention	39	35.2 ± 7.2	21.5	Yes	11.8%	GDM controlled % macrosomia in subjects gaining weight—17.9% Vs. losing/no change—4.2%
	Diet	57	33.5 ± 9.2	29.8	No	15.2%	
2. Barakat (2012) ⁵⁰	Intervention	40	22.7 ± 2.8	12.5 ± 3.2	No	No	No GDM
	Control	43	23.0 ± 2.9	13.8 ± 3.1		No	Three subjects with GDM
3. de Barros (2010) ⁵³	Intervention	32	29.6 ± 4.1	30.4 ± 4.3	No	3.1	Resistance exercise
	Control	32	29.4 ± 4.0	29.9 ± 4.1		9.4	
4. Bo S (2014) ⁵⁴	Intervention	101	27.6 ± 4.1	NA	Yes	9.9%	Exercise but not behavior improved post prenatal glucose
	Behavior	99	27.5 ± 4.2	NA	No		
5. Bung et al. (1991) ⁴⁶	Intervention	17	35.2 ± 4.8	NA	No	10.1%	Exercise and diet as efficient as insulin for GDM management
	Insulin	17	35.9 ± 3.9	NA	—	11.7%	
6. Dempsey (2004) ⁵⁷	Intervention		Continuous, categorical, and multivariable models	NR	Yes	NR	74% lower GDM risk 56% lower GDM risk
	≥6 hours/week	326					
	≤6 hours/week	289					
7. Hopkins (2009) ⁵⁹	Intervention	47	26.7	NR	Yes	4.3%	No effect on insulin sensitivity in either group Self-reported compliance Lower cord IGF—1 in exercise subjects
	Control	37	25.5		No	5.4%	
8. Asbee (2009) ⁶⁰	Intervention	57	25.5	25.1	No	NR	C/S 25%
	Control	43	25.6	40.1	No	NR	C/S 58.3%
9. Kinnunen (2012) ⁶¹	Intervention	128	>25	46.8% (above recommendation)	Yes	2.7%	No difference in GDM GDM—15.8% GDM—12.4% LGA—reduced in both groups Physical activity not quantified
	Control	110	>25	54.4% (above recommendation)	No	2.8%	

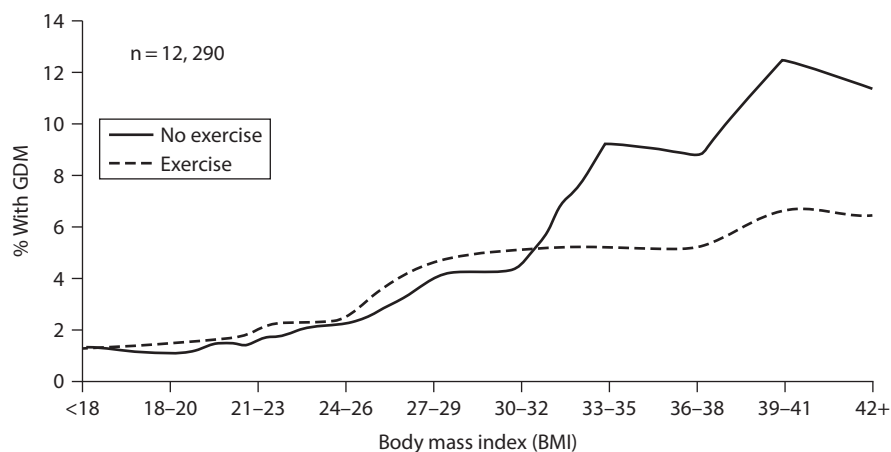
^a LGA, large for gestational age.^b GWG, gestational weight gain.**Figure 33.3** Prevalence of GDM by BMI and Physical Activity Status 1995–1996 (Central New York). (From Dye, T.D. et al., *Am. J. Epidemiol.*, 146(11), 961, 1997. With permission.)

Table 33.3 Exercise prescription for sedentary, overweight, or obese women with GDM who are unaccustomed to exercise

Previously sedentary and/or overweight/obese pregnant women	RPE ^a	Target exercise energy expenditure (MET hours/week)
Weeks 1–3 of training	12–14	≥16
Weeks 3–6 of training	13–15	28
Weeks 6–9 GA ^b of training	15–16	28

^a RPE, rate of perceived exertion 6 equals no exertion and 20 equals maximal exertion.
^b GA, gestational age.

- Exercise or limited gestational weight gain or in combination can reduce the risk of gestational diabetes.
- A daily exercise routine of at least 30 minutes/day can prevent or improve hyperglycemia.
- Pregnancy is an ideal time for behavioral modifications, since patients are under frequent and close supervision.

Research agenda

- Cost-effectiveness in obesity and diabetes prevention.
- When are interventions likely best prevent gestational diabetes?
- The role of educators and healthcare providers in instilling lifelong healthy behavior to prevent obesity and comorbidities.

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34 Role of bariatric surgery in obese women planning pregnancy

Ron Charach and Eyal Sheiner

Introduction

Obesity is an epidemic affecting both developed and developing countries and is defined as prepregnancy body mass index (BMI) ≥ 30 kg/m².¹ Excessive weight gain and obesity as a chronic disease are considered to be two of the most pressing concerns in the developed world due to their growing threat to health in countries all over the world. The prevalence of overweight and obesity has increased dramatically with alarming rates over the recent decades and has nearly doubled since 1980.^{2–4} In 2008, more than 1.4 billion adults 20 years and older were overweight. Of these, nearly 300 million women were obese.⁴ In the United States, nearly 35% of adults were obese and over one-third of women 20 years and older were obese in 2011–2012.⁵ Excessive weight gain and obesity is the fifth leading risk for global deaths, and according to the latest WHO fact sheet, at least 2.8 million adults die each year as a result of being overweight or obese. Obesity and excessive weight gain may also contribute substantially to the burden of chronic health conditions such as diabetes, ischemic heart disease, stroke, respiratory problems, certain cancers (endometrial, breast, and colon), and osteoarthritis.^{4,6} In concordance to this worldwide increase in the prevalence of overweight and obesity, close to one-third of women of childbearing age (20–39 years) are classified as obese, and an additional quarter of women in this age group are overweight.^{3,7,8} Those disturbing findings can eventually lead to adverse consequences for their future reproductive health, pregnancy, and long-term health.⁹ Significant reduction in obesity-related reproductive complications may be achieved by weight loss. Surgical treatment has a great potential to treat obesity in women of reproductive age, as Sjostrom reported bariatric surgery to be the most efficient means of weight loss in severely obese patients.¹⁰

This chapter attempts to review the most recent available data on the role of bariatric surgery in the obese pregnant woman and discusses the management and outcomes

of postbariatric surgery parturients. This chapter addresses the safety of bariatric procedures in pregnancy as compared to the general population and whether it is safer than pregnancy in the obese. General clinical guidelines and recommendations are provided throughout the text.

Obesity impacts on pregnancy and fertility (Table 34.1)

Fertility and infertility treatments

Obesity appears to be associated with reduced fecundity rates and increased time to pregnancy. Van der Steeg et al.¹¹ reported that obese women, even with a regular cycle, with a BMI over 29 kg/m² have lower pregnancy rates compared with those with normal weight. Other studies also found an association between obesity and reduced fecundity and suggested that weight loss could increase fecundity for overweight and obese women.^{12,13} Not all studies are consistent regarding infertility treatments in obese women. Several studies have shown that higher BMI was inversely related to follicular growth in response to gonadotropins and is associated with reduced probability of achieving pregnancy in women receiving assisted reproduction.^{14–16} Other studies argued that although higher threshold dose of gonadotropins and more days of stimulation were required, there is no difference in the overall outcome and success of treatment cycles in comparison to normal-weight women.^{17,18} In a systemic review of 33 studies including almost 48,000 treatment cycles of in vitro fertilization or intracytoplasmic sperm injection treatments in women who were overweight or obese (BMI > 25), significantly higher miscarriage rate (relative risk, RR = 1.31, $p < 0.0001$) as well as lower clinical pregnancy (RR = 0.90, $p < 0.0001$), and live birth rates (RR = 0.84, $p = 0.0002$) were found compared to women with normal weight (BMI < 25).¹⁹

Table 34.1 Adverse fertility and pregnancy outcomes found to be associated with obesity*Fertility*

- Reduced fecundity
- Higher threshold for successful gonadotropin treatments
- Lower clinical pregnancy rate

Antepartum

- Spontaneous abortion
- Gestational diabetes mellitus
- Pregnancy-induced hypertension
- Exacerbation of chronic maternal diseases

Intrapartum and postpartum

- Longer first stage of labor
- Increased risk of cesarean delivery
- Anesthesia complications
- Wound disruption
- Infection
- Deep venous thromboembolism
- Postpartum hemorrhage

Perinatal

- Congenital malformations (especially neural tube defects)
- Fetal and early neonatal death
- Large for gestational age
- Shoulder dystocia
- Future metabolic syndrome

Antepartum complications

Pregestational maternal obesity is known to be a significant risk factor for adverse outcomes during pregnancy.^{20–22} During early pregnancy, there is an increased risk for spontaneous abortion.²³ In a systematic review of 16 studies, patients with a BMI of ≥ 25 kg/m² had significantly higher risk of abortion (odds ratio [OR], 1.67).²⁴ Later during pregnancy, maternal metabolic manifestations of obesity and metabolic syndrome may be apparent.

A higher prevalence of gestational diabetes mellitus (GDM) and pregnancy-induced hypertension (PIH) was found in obese women.^{20–23,25–27} A dose-dependent effect has also been demonstrated between increasing maternal BMI and risk for GDM and PIH.^{27,28}

In obese gravidas, physiologic changes during pregnancy may exacerbate maternal chronic problems such as sleep apnea, nonalcoholic fatty liver disease, and cardiac or renal dysfunction.²⁹

Intrapartum and postpartum complications

During intrapartum, it appears that in overweight and obese women, first-stage labor progression is significantly slower than that of normal-weight women.^{30–34} Moreover, labor proceeds more slowly as BMI increases.^{30–34} Vahratian et al., in a cohort study of 612 nulliparous women, found that the median duration of labor from 4 to 10 cm was significantly longer for both overweight and obese women, compared to normal-weight women (7.5, 7.9, and 6.2 hours, respectively).³⁴ The obese patient is also at an increased risk of both elective and

emergency cesarean delivery (CD), and this risk increases with increasing obesity.^{22,35,36} High rates of associated anesthesia complications, wound disruption, infection, and deep venous thromboembolism were also found in obese parturient.^{21,37–39}

Whether obese woman are at increased risk for postpartum hemorrhage is a matter of controversy. While several small studies did not find an association,^{25,40,41} Sebire et al., in a population-based cohort study, reported a 30% increased risk for a major postpartum hemorrhage (PPH) in gravidas with moderately raised BMI and about 70% increased risk for women with very raised BMI compared with women of normal BMI.⁴²

Perinatal complications

Adverse perinatal outcomes may be associated with overweight and obesity. Maternal obesity appears to be associated with an increase in the rates of some congenital malformations (especially neural tube defects [NTDs]), and the risk may increase with increasing maternal weight.^{43–45} In a systematic review (39 studies) and meta-analysis (18 studies), Stothard et al.⁴⁴ reported that maternal obesity is likely to be associated with a small increased risk of a range of structural anomalies such as spina bifida, NTD, cardiovascular anomalies, septal anomalies, cleft palate, cleft lip and palate, anorectal atresia, hydrocephaly, and limb reduction anomalies. It should be emphasized that these findings may be partially explained by technical problems with ultrasound detection (reducing rates of early terminations) and lower folic acid levels (body distribution).^{46,47}

Maternal obesity has consistently been associated with increased rates of fetal and early neonatal death. Chu et al.,⁴⁸ in a meta-analysis of nine controlled studies, reported that maternal obesity is associated with an increased risk of stillbirth in comparison to normal-weight women. The mechanism of fetal compromise has not been fully determined and is likely to be multifactorial. Neonatal death may be caused largely due to pregnancy complications leading to preterm birth or other disorders.⁴⁹

Several studies have shown that pregestational maternal obesity and excessive weight gain during pregnancy are independent risk factors⁵⁰ for macrosomic (>4000 g) or large-for-gestational-age (LGA) neonates.^{22,25,37,40,51,52} Increasing prepregnancy weight and maternal BMI has a linear relationship with birth weight and macrosomia.^{52–54} One potential sequela of fetal LGA might be shoulder dystocia (SD). Indeed, several studies found that the risk for SD increased with increased maternal BMI.^{20,55}

Long-term complication and metabolic programming

Recently, there is growing evidence in epidemiological studies and animal models that embryonic, fetal, and early postnatal subtle environment effects might appear as health issues later in life (i.e., obesity, type 2 diabetes mellitus). These effects are known to be designated as metabolic programming.^{56,57} Laitinen et al.⁵⁸ reported that offspring of overweight or obese mothers had higher mean BMIs at each age point tested than did children born to underweight or

normal-weight mothers. Children exposure to maternal obesity posed a strong predictor for significant risk of future metabolic syndrome.⁵⁹ Hochner et al.⁶⁰ found that maternal size both before and during pregnancy was also associated with cardiometabolic risk factors in young adult offspring.

Treating obesity: What are the options?

It is strongly advised to encourage obese women to undertake a preconception assessment, counseling, and weight reduction program.¹ Preconception weight reduction has been proven to be the best way to decrease medical and obstetric complications in obese women planning pregnancy.^{61,62} Currently, there are two main options for obesity treatment: nonsurgical treatment and bariatric surgery. Nonsurgical treatment is usually multicomponent and includes dietary changes, exercise, behavior modification, and various pharmacotherapies. Until recently, observational studies and randomized controlled trials were not powered enough to detect differences between those two approaches on multiple health outcomes. In 2007, Sjöström¹⁰ conducted the Swedish Obese Subjects study, which is currently one of the best sources of evidence regarding long-term consequences of bariatric surgery. This prospective, non-randomized trial included 4047 obese persons, of which 2010 individuals underwent bariatric surgery and 2037 matched controls were given conventional treatment. Maximal weight loss after bariatric surgery was achieved after 1–2 years and was in average 32% for gastric bypass, 25% for vertical-banded gastroplasty (VBG), and 20% for gastric banding. These findings were opposed to body weight change of only 1%–2% for the conventional treatment group.¹⁰ After 10 years, the weight losses were, respectively, 25%, 16%, and 14% in average and were maintained also in the 15 years' follow-up. The authors concluded that surgery is the *only* effective treatment for obesity with a dramatic positive effects on most cardiovascular risk factors and type 2 diabetes mellitus and with significant reduction of mortality (adjusted hazards ratio of 0.71, $p = 0.01$).¹⁰ Likewise, a recent meta-analysis that included 11 studies with 796 individuals (range of mean BMI at baseline 30–52) demonstrated that bariatric surgery is more efficient than nonsurgical treatment for obesity for up to 2 years of follow-up. Higher rates of body weight reduction and remission of type 2 diabetes and metabolic syndrome were found in the bariatric surgery group.⁶³ Nevertheless, it should be emphasized that bariatric surgery could also lead to some postoperative complications such as iron-deficiency anemia (mainly in malabsorptive bariatric surgery) and reoperations.⁶³

Given the limited long-term success of lifestyle modifications and medical treatments, rates of surgical weight loss procedures have increased dramatically over the recent decade.

Between the years 1998 and 2005, the incidence of bariatric surgery in the United States has increased by 800%.⁶⁴ In women within the 18 to 45 years age group, it has accounted for 83% of procedures.⁶⁴ Those findings stress the need to address this new obstetric group with unique risks and possible fetal and maternal outcomes.

Types of bariatric procedures

To date, there are three fundamental types of bariatric surgical procedures: (1) malabsorptive, (2) restrictive, and (3) procedures with both a restrictive and malabsorptive component (Table 34.2).

Malabsorptive procedures

Pure malabsorptive procedures, such as biliopancreatic diversion (BPD) and jejunoileal bypass, cause weight loss primarily by decreasing the absorption of nutrients either through diversion of the biliopancreatic secretions that are essential for the absorption of micronutrients or bypassing a significant portion of small bowel surface area. This type of procedures can bring about superior weight loss results, but they may also bring about serious metabolic complications and micronutrient deficiencies. Due to their complexity and the linkage to significant safety concerns, they are now rarely performed.⁶⁵

Restrictive procedures

Restrictive procedures, such as laparoscopic adjustable gastric banding (LAGB), VBG, and probably also sleeve gastrectomy (with controversy), are frequently performed in the United States and Europe.⁶⁶ The least invasive procedure is LAGB, which is completely reversible and has the lowest mortality rates.⁶⁵ In this procedure, a fluid-filled band is placed around the stomach near the fundus, reducing gastric volume, reservoir capacity, and eventually solid food intake. Although these procedures are simpler and safer in comparison to malabsorptive procedures, they tend to produce more gradual weight loss and have the disadvantages of frequent office visits for band adjustment and that some high-energy foods (soft solids and liquid) may bypass the restriction.

Mixed procedures: Combination of restriction and malabsorption

The most commonly performed procedure in the world is currently of the combined type with the Roux-en-Y gastric bypass (RYGB) accounting for 46.6% of all bariatric procedures.⁶⁶ In the RYGB, a small gastric pouch restricts oral intake, and small bowel reconfiguration provides additional mild malabsorption and neuroendocrine changes favoring weight loss.⁶⁵

Table 34.2 Types of bariatric procedures

Malabsorptive

- Biliopancreatic diversion
- Jejunoileal bypass
- Biliopancreatic diversion with duodenal switch

Restrictive

- Laparoscopic adjustable gastric band
- Vertical banded gastroplasty
- Sleeve gastrectomy (may also have malabsorptive effect)

Mixed procedures

- Roux-en-Y gastric bypass

General outcomes

Inconsistency exists regarding the long-term outcomes of different types of bariatric surgery. A recent systematic review of all bariatric procedures with a follow-up of 10 or more years showed greater than 50% excess weight loss for all current procedures. The weight losses for LAGB and other bariatric procedures were substantial and with similar excess weight loss in the long term.⁶⁷ Angrisani et al., however, in a recent study that compared outcomes of patients randomly assigned to undergo LAGB or RYGB at 10 years, reported that RYGB had better results than LAGB in terms of excess weight loss results (76.2% vs. 46.2%) at 10 years' follow-up.⁶⁸ Nevertheless, LAGB was found to be safer in terms of early and long-term surgical complication.⁶⁸

Postbariatric surgery: Pregnancy complications and management

Since concerns arose regarding the potential impact of bariatric surgery on future pregnancies, a multidisciplinary team approach of a bariatric surgeon and a maternal–fetal medicine specialist is probably the best way to manage subsequent pregnancies. Special concern should be given to screening for gestational diabetes, nutritional guidelines and supplementation, gastrointestinal complaints, and gravidas who still remain obese during pregnancy.⁶⁹ For the appropriate management of postbariatric pregnancy, see Table 34.3.

Nutritional deficiencies

Several case studies have demonstrated nutritional deficiencies in postoperative pregnancies.^{70–72} Procedures involving malabsorption, such as RYGB, appear more likely to cause nutritional deficiencies due to hormonal and nutritional changes as compared to purely restrictive procedures such as LAGB. Although only one case of anemia was demonstrated in a study of 79 consecutively enrolled, previously banded pregnant patients,⁷⁰ all types of bariatric surgery may be complicated by iron deficiency. Malabsorptive procedures may be more refractory to treatment and are also prone to be associated with an increased risk of calcium, vitamin D, and vitamin B12 deficiencies.⁷³ Therefore, prenatal and perinatal

oral iron treatments along with multivitamin, folate, and B12 supplementation are imperative. Gurewitsch et al.⁷⁴ even proposed that female patients who had RYGB in the child-bearing age should undergo preconception treatment with parenteral iron to avoid the risks of transfusion therapy during pregnancy.

Marceau et al.⁷⁵ reported a significant decrease in mean serum albumin concentration among women after BPD, with 1.6% of them requiring parenteral nutrition. Eerdekens et al.⁷⁶ described five case reports of postoperative excessive vomiting or fat malabsorption that eventually resulted in severe vitamin K deficiency and fetal cerebral hemorrhage. Other case reports have described NTD possibly related to folate deficiency,⁷⁷ fetomaternal electrolyte imbalances,⁷⁸ and microphthalmia attributed to vitamin A deficiency.⁷⁹

In light of these findings, regardless of the type of bariatric procedure, routine nutritional screening, recommendations for appropriate supplements, and monitoring compliance of this unique population are obligatory.⁷³ Concerns about low birth weight caused by malnourishment of mother and fetus are discussed later in this chapter.

Screening for gestational diabetes mellitus

Glucose screening in several postoperative patients should be managed differently as compared to the general population. Glucose challenge test (GCT) or glucose tolerance test are not well tolerated in those patients who have undergone a procedure with malabsorptive component such as RYGB, due to the “dumping syndrome” that occurs in approximately 50% of these patients.⁸⁰ “Dumping syndrome” is caused by ingestion of high amounts of refined sugars that leads to a hyperosmolar environment and fluid shift from the intravascular compartment to the small bowel lumen, causing distension, cramping, nausea, vomiting, and diarrhea. Reasonable alternatives for screening are measuring glycated hemoglobin (A1C) and assuming overt diabetes is present if it is elevated ($\geq 6.5\%$) and measuring fasting and postprandial blood sugars for 1–2 weeks in the second trimester.^{81,82} Restrictive-type bariatric procedures such as LAGB are not reported to cause dumping syndrome; therefore, women after LAGB procedure can undergo standard testing for GDM.

Gastrointestinal complications

Life-threatening surgical complications of both malabsorptive and restrictive procedures might be nonspecific, resemble a number of other conditions, and could be difficult for obstetricians to recognize. For this reason, all pregnant women with a history of bariatric surgery with severe abdominal pain should also be examined by a general surgeon.

Bowel obstruction during pregnancy in women who had previously undergone bariatric surgery has been reported in several case reports, and few of them reported fetal and maternal deaths.^{83,84} In those patients, common obstetric complaints such as hyperemesis, esophageal reflux, and contractions might mimic early bowel obstruction symptoms and should be

Table 34.3 Appropriate management of postbariatric pregnancy

- Routine screening for nutritional deficiencies
- Usage of appropriate supplements and monitoring compliance
- Alternative screening ways for GDM (after malabsorptive procedure)
- Careful evaluation by a general surgeon in cases of severe abdominal pain
- Avoidance of conception for 12 months following bariatric surgery

evaluated carefully. Most cases are attributed to bowel ischemia and internal hernia formation after RYGB.^{84–87} The estimated prevalence of this complication is up to 2%, and it is contributed by elevated abdominal pressure and cephalad intestinal displacement caused by the enlarging gravid uterus.⁸⁴ Computed tomography scan and even exploratory surgery may be necessary in highly suspicious clinical circumstance.^{81,88}

Among women who have undergone LAGB, band slip-page has been reported in the literature^{89,90}; nevertheless, as other postbariatric surgical complications, systematic studies have not reported high rates of this complication. Haward et al.⁹¹ recently demonstrated that pregnancy does not increase the risk of primary or overall band revision after LAGB. However, the authors mention that shorter time between LAGB operation and pregnancy may predispose to band revisions ($p = 0.03$).

One of the major benefits of LAGB is the band adjustability that allows varying degrees of weight reduction or gain and control of gastrointestinal symptoms such as nausea and vomiting. Some surgeons prophylactically adjust the band: Ducarme et al.⁹² demonstrated a 60% band adjustment rate for the prevention of nausea and vomiting in the first trimester of pregnancy. However, Martin et al.⁹³ reported that although some bands were adjusted to alleviate nausea and vomiting, the gastric bands were not routinely deflated during pregnancy. Dixon et al.⁷⁰ found that patients often required close monitoring and band adjustment in order to meet the recommended gestational weight gain and to relieve excessive nausea and vomiting. They also reported that some fluid was removed at 36 weeks in order to reduce the risk of gastric restriction during delivery. Currently, there is no general practical consensus as to whether or not bands should be deflated once pregnancy is detected.

Gestational weight gain

Currently, there are no clear guidelines for optimal weight gain during pregnancy in women who have undergone bariatric surgery. Nutritionist consultation after conception is important for the planning of dietary regimens that are adjusted to the physiologic changes of pregnancy. Weight gain recommendations are based on Institute of Medicine (IOM) guidelines, which are based on prepregnancy BMI.⁸² The minimum weight gain standards suggested by the IOM are 230 g/week for obese women in the second and third trimester. Dixon et al. reported that if the bariatric surgery team monitored the patient throughout the pregnancy, the weight gain was optimal and similar to the IOM recommendations.⁷⁰ Due to concerns about fetal growth, caloric restriction during pregnancy is not recommended even in the price of continuing to be overweight after bariatric surgery.⁸²

Surgery-to-conception interval

After bariatric surgery, the first 1–2 years is often referred to as the “rapid weight loss phase.”^{82,94} During this period of time, fertility may be increased and effectiveness of certain contraceptives may be decreased, possibly leading to

high number of unintended pregnancies.^{95,96} Theoretically, conception during this time period provokes a risk for surgical complications, nutritional-related complications, and malformations.⁹⁷ It seems reasonable that additional nutritional requirements of the developing fetus and the dramatic decline in maternal intake of nutrition might lead to intrauterine growth restriction (IUGR).⁹⁸ When considering the consequences of early postbariatric pregnancies, the following issues should be addressed:

1. *Pregnancy outcome and safety:* In order to optimize weight loss and reduce the potentially adverse effects of nutrient fluctuations and deficiencies after surgery,^{75,81,88} women are currently advised to avoid conception for 12–18 and sometimes 24 months following bariatric surgery.^{64,82,88,94,99,100} The 2009 ACOG Practice Bulletin on pregnancy after bariatric surgery advised that “some authorities have recommended waiting 12–24 months after bariatric surgery before conceiving so that the fetus is not exposed to a rapid weight loss environment and so that the patient can achieve full weight loss goals.”⁸² This undetermined advice reflects the growing numbers of observational studies that do not demonstrate a difference in pregnancy outcomes in early postbariatric surgery gestations as compared to later ones.^{70,101–103} Our group¹⁰⁰ compared the pregnancy outcome of 104 patients who conceived during the first postoperative year to 385 patients who conceived after the first postoperative year. No significant difference was found between the two groups nor was a shorter time interval to conception associated with an adverse perinatal outcome or pregnancy complications. As a possible explanation, Kral et al.¹⁰⁴ suggested that in oppose to starvation state, the lack of abnormal starvation stress after bariatric surgery does not expose the fetus to an excess of glucocorticoids, therefore being less likely to induce IUGR in the neonate. In light of the theoretical risks raised, avoiding pregnancy for at least 1 year is still advised, but if conception does occur less than a year after surgery, advising termination of the pregnancy seems to be unnecessary due to the relative scarcity of complications uncovered to date. Close observation alone may be sufficient to achieve a satisfactory outcome.
2. *Pregnancy weight gain and postpartum weight loss:* Currently, inconsistency exists regarding the effect of early pregnancy after surgery on gestational weight gain and postpartum weight loss. Dao et al.¹⁰¹ reported that women who conceived within 12 months of surgery had less weight gain during pregnancy and less weight loss postpartum than those who waited longer before conceiving (mean gestational weight gain 1.8 vs. 15.5 kg). However, Wax et al.¹⁰³ compared 52 postgastric bypass patients with surgery-to-conception intervals of ≤ 18 months to those of > 18 months and found no statistically significant differences in maternal pregnancy weight gain. Only limited data are available on the long-term effects of time to conception after surgery on total weight loss with some studies reporting no negative effect on total weight loss.^{101,105}

Table 34.4 Summary of selected studies on gestational diabetes mellitus in pregnancy after bariatric surgery

Study (author, year, country)	Cases	Comparison group	Type of surgery	Main findings
Lesko and Peaceman ¹²⁶ 2012, USA	70 deliveries	140 deliveries matched for presurgical BMI $\pm$ 6	BS (85.7% RYGB)	Significant decrease in rate of GDM in BS patients (0%) as compared with control groups (morbidly obese 16.4%, obese 9.3%).
Sheiner et al. ¹¹¹ 2004, Israel	298 deliveries	Pregnancy cohort without BS, $n = 158,912$	BS	Higher rate of GDM in postsurgical patients as compared to the general population. <i>No association</i> when confounders were eliminated by logistic regression analysis.
Ducarme et al. ⁹² 2007, France	13 deliveries	414 deliveries in obese women	LAGB	Decreased rate of GDM post-LAGB as compared to obese controls (0% vs. 22.1%).
Aricha-Tamir et al. ²⁹ 2012, Israel	144 deliveries	144 presurgical deliveries in the same women	BS (3.4% RYGB)	Decreased risk for diabetes mellitus postsurgery (significant for the total procedures, mainly LAGB) (OR 0.2).
Dixon et al. ⁷⁰ 2005, Australia	79 deliveries	79 deliveries matched for BMI, age, and parity	LAGB	Lower rate of GDM after LAGB as compared to obese controls (6.3% vs. 19%).
Burke et al. ¹⁰⁸ 2010, USA	354 deliveries	346 presurgical deliveries	BS (87%/75% RYGB)	Women with delivery after BS had lower incidences of GDM (8% vs. 27%, OR 0.23).
Weintraub et al. ¹⁰⁷ 2008, Israel	507 deliveries	301 presurgical deliveries	LAGB	Decreased risk for diabetes mellitus after BS compared to presurgical deliveries.
Skull et al. ¹¹⁴ 2004, Australia	49 deliveries (44 women)	31 presurgical deliveries in the same women	LAGB	Incidence of GDM was significantly reduced in the LAGB group (8% vs. 27% $p = 0.048$).
Patel et al. ¹⁰² 2008, USA	26 deliveries	254 deliveries stratified by BMI	RYGB	NS
Wax et al. ¹⁰³ 2008, USA	38 deliveries	76 deliveries matched for maternal age and prior CS	RYGB	NS

Abbreviations: BS, bariatric surgery; CS, cesarean section; LAGB, laparoscopic adjustable gastric banding; NS, no significant difference; RYGB, Roux-en-Y gastric bypass.

Obstetric outcomes

Gestational diabetes mellitus (Table 34.4)

Obese women clearly have an increased risk for developing GDM¹⁰⁶ making surgical weight loss procedures a potentially good way to prevent it.

Weintraub et al.¹⁰⁷ in a retrospective study that compared pregnancy outcomes of 301 pregnancies before bariatric surgery to 507 pregnancies after bariatric surgery, Weintraub et al.¹⁰⁷ found that there was a significantly lower prevalence of GDM in the postbariatric surgery group (17.3% vs. 11.0%, respectively). Similar results were observed by Burke et al.¹⁰⁸ in a recent retrospective study comparing 346 women who had deliveries before bariatric surgery to 354 women who had deliveries after bariatric surgery. In their study, the incidences of GDM in the postbariatric group was even equivalent to the general population (8% vs. 27%, OR 0.23, 95% confidence interval [CI] 0.15–0.36).¹⁰⁹ Other observational studies consistently report a lower prevalence of GDM among women who have had bariatric surgery than among obese women who have not undergone this surgery¹¹⁰ (Figure 34.1). However, when

298 postoperative deliveries were compared to 158,912 deliveries of the general population by Sheiner et al., a higher rate of GDM was found among women who underwent bariatric surgery (9.4% vs. 5.0%, $p = 0.001$).¹¹¹ It was because the postoperative women were still more likely to be obese, as compared with the general population. No significantly increased risk for GDM in postoperative women was found after confounders such as maternal BMI were neutralized. Other studies have also found higher prevalence of GDM among postoperative women in comparison to the general population.^{112–114} Clinicians can be reassured that women with a history of bariatric surgery who eventually develop GDM during subsequent pregnancies appear to have similar perinatal outcomes and glycemic control as other women with GDM.¹¹⁵

To date, despite the controversial magnitude of its effect, it seems that bariatric surgery does, in fact, lower the risk of GDM in subsequent pregnancies, although this risk does not completely normalize to general population levels, perhaps due to residual obesity among postoperative women. Whether the type of bariatric procedure impacts the course and outcome of GDM is unclear.

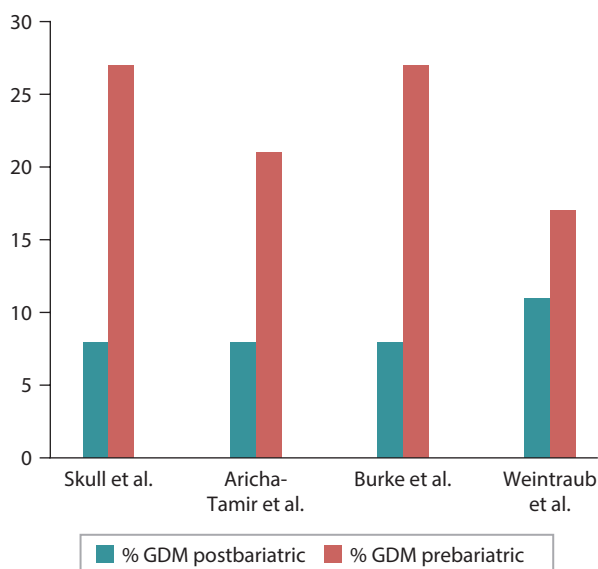


Figure 34.1 Selected studies presenting rates of gestational diabetes mellitus before and after bariatric surgery.

In postoperative women with type 2 diabetes who reduced body weight and normalized serum glucose before pregnancy, euglycemia may remain during pregnancy despite pregnancy-related insulin resistance.¹¹⁶

Hypertensive disorders (Table 34.5)

Obesity is a known risk factor for the development of hypertensive disorders of pregnancy, and it has been consistently reported that maternal weight and BMI are independent risk factors for preeclampsia, as well as other hypertensive disorders.^{21,106,117–119}

Studies among postbariatric surgery women as compared to obese controls that examined this spectrum of outcomes have generally demonstrated them to be lower in postoperative women.^{70,107,115,120} Aricha-Tamir et al.,²⁹ in a recent study of 288 women (144 preoperative pregnancies that were matched to 144 postoperative pregnancies of the same women), found a significant reduction in hypertensive disorders in postoperative pregnancies (adjusted OR 0.4, 95% CI 0.2–0.8). Bennett et al.¹¹⁹ reported that women who delivered after surgery had substantially lower rates of preeclampsia and eclampsia (OR 0.20, 95% CI 0.09–0.44), chronic hypertension complicating pregnancy (0.39, 0.20–0.74), and gestational hypertension (0.16, 0.07–0.37). These lower rates remained even after adjustment for age at delivery, surgical procedure, and preexisting diabetes (Figure 34.2).

Sheiner et al. revealed no difference in the risk for hypertensive disorders among pregnancies subsequent to restrictive versus malabsorptive-type procedures.⁹⁹

Finally, studies comparing the risk for hypertensive disorders in postoperative women and general population controls found that the incidence of preeclampsia may drop down to be the same as the general obstetrical community.^{103,111,121}

Mode of delivery (Table 34.6)

Obese patients are at increased risk of both elective and emergency CD, and this risk increases with increasing obesity.^{22,36,122} When compared to the general obstetric population, observational studies reported higher CD rates in postbariatric surgery pregnancies.^{102,111} This is not surprising and could be explained by the fact that postoperative patients are typically older and more likely to be obese than women in the general obstetrical population.^{103,115} Sheiner et al.²² also suggested that this higher prevalence of cesarean section seen in postoperative patients may be explained by caregiver bias, mentioning that clinicians should have a clear indication before operating these patients.

Postoperative patients tend to have either similar or lower rate of CD compared to obese women who have not undergone bariatric surgery.^{102,123}

Fetal outcomes

Birth weight (Table 34.7)

Inappropriate maternal weight gain (especially during the rapid weight loss phase of the first 1–2 years postsurgery) along with the elevated risk of nutritional deficiencies stresses the need for careful monitoring for fetal growth in postbariatric surgery patients.

Compared with obese women who have not undergone a bariatric procedure, observational studies have generally reported larger proportion of appropriate-for-gestational-age infants among postbariatric surgery pregnancies.^{75,102,107}

LGA: Maternal obesity and excessive weight gain during pregnancy are associated with macrosomic (>4000 g) or LGA neonates.¹²⁴ Most studies comparing postbariatric surgery pregnancies to pregnancies in obese women have found decreased rates of LGA or macrosomic infants.^{64,75,92,123,125} Weintraub et al.¹⁰⁷ reported a *reduction* of more than 50% in the prevalence of macrosomia (OR 0.45; 95% CI 0.21–0.94). When comparing postoperative pregnancies to the general population, there was no consistent reduction in the rates of LGA and macrosomic infants.^{103,111} This could be explained perhaps by the fact that postoperative women tend to be more obese than women in the general population, thereby still maintaining a higher risk for macrosomia. These data suggest that rates of fetal macrosomia in subsequent pregnancies may be reduced by weight loss after bariatric surgery.

Growth restriction: Although inconsistent, some observational studies have demonstrated *increased* rates of IUGR and small-for-gestational-age (SGA) infants in postbariatric surgery patients.^{75,111,121,123,125,126} A recent population-based study from Denmark,¹²³ conducted among infants born after maternal bariatric surgery (84% gastric bypass), revealed 2.3 times higher risk of SGA than infants born by a matched group of women (prepregnancy BMI, age, parity, date of delivery, and smoking) without bariatric surgery. Substantial maternal

Table 34.5 Summary of selected studies on hypertensive disorders in pregnancy after bariatric surgery

Study (author, year, country)	Cases	Comparison group	Type of surgery	Main findings
Sheiner et al. ¹¹¹ 2004, Israel	298 deliveries	Pregnancy cohort without BS, <i>n</i> = 158,912	BS	• No difference in rate of mild preeclampsia and severe preeclampsia among postsurgical women and normal controls. • Increased risk for chronic hypertension in postsurgical women. • No increased risk of total hypertensive disorders based on multivariate logistic regression.
Ducarme et al. ⁹² 2007, France	13 deliveries	414 deliveries in obese women	LAGB	• Decreased rate of preeclampsia in post-LAGB as compared to obese controls (0% vs. 3.1%). • NS in PIH.
Aricha-Tamir et al. ²⁹ 2011, Israel	144 deliveries	144 presurgical deliveries in the same women	BS (3.4% RYGB)	Decreased risk for hypertensive disorders among postsurgical (mainly LAGB) deliveries as compared to presurgical deliveries of the same women (OR 0.4).
Dixon et al. ⁷⁰ 2005, Australia	79 deliveries	1. 40 presurgical deliveries in the same women 2. 79 deliveries matched for BMI, age, and parity 3. Community	LAGB	• Lower rate of PIH and preeclampsia among post-LAGB women as compared to obese controls (10% vs. 38% and 5% vs. 25%, respectively) and preoperative pregnancies (10% vs. 45% and 5% vs. 28%, respectively). • NS in PIH as compared to community.
Bennett et al. ¹¹⁹ 2010, USA	316 deliveries	269 presurgical deliveries	BS (84% RYGB)	Women who delivered after surgery had substantially lower rates of preeclampsia and eclampsia (OR 0.20), chronic hypertension complicating pregnancy (OR 0.39), and gestational hypertension (OR 0.16) even after adjustment for age at delivery, multiple pregnancy, surgical procedure, preexisting diabetes, and insurance plan.
Weintraub et al. ¹⁰⁷ 2008, Israel	507 deliveries	301 presurgical deliveries	LAGB	Decreased risk for total hypertensive disorders and severe preeclampsia in postsurgical as compared to presurgical deliveries (OR 0.4).
Patel et al. ¹⁰² 2008, USA	26 deliveries	254 deliveries stratified by BMI	RYGB	NS
Wax et al. ¹⁰³ 2008, USA	38 deliveries	76 deliveries matched for maternal age and prior CS	RYGB	Increased rate of hypertension among post-RYGB women and age-/prior cesarean section-matched controls; however, the increased risk was eliminated once BMI was controlled for.

Abbreviations: BS, bariatric surgery; CS, cesarean section; LAGB, laparoscopic adjustable gastric banding; NS, no significant difference was found; OR, odds ratio; PIH, pregnancy-induced hypertension; RYGB, Roux-en-Y gastric bypass.

weight loss and induced malabsorption were thought by the authors as the reason for the increase in SGA births. When compared to the morbidly obese group, Lesko and Peaceman,¹²⁶ in a recent study, found that neonates of postoperative women were significantly more likely to be SGA (5.0% vs. 17.4%, respectively). Similar results were demonstrated by our group¹¹¹ in a study among postoperative women (procedures of all types) and the general obstetric population (5% vs. 2%, respectively). However, when variables such as obesity and hypertensive disorders were controlled, this relationship disappeared. This may highlight the importance of residual confounders when interpreting the results of studies commenting on SGA or IUGR in postoperative pregnancies.

In contrast, in a small study including 13 post-LAGB patients, Ducarme et al. reported a decreased rate of delivering

an SGA infant (<2500 g) among post-LAGB patients versus obese controls. The authors hypothesized that this improved outcome may be related to the reduction in the risk of preeclampsia. Another study comparing 38 post-RYGB cases with 76 general population controls found no difference in mean birth weight or IUGR among the two groups.¹⁰³

Congenital anomalies (Table 34.8)

Although deficiencies in a number of nutrients have been reported in case studies^{68–70} and concerns about malnourishment of mother and fetus were made, systematic studies have repeatedly failed to link history of bariatric surgery with poor perinatal outcomes.^{75,92,107,111} Increased risk of congenital anomalies has been found in general in overweight and obese women, and postbariatric surgery patients must be balanced with this known risk.

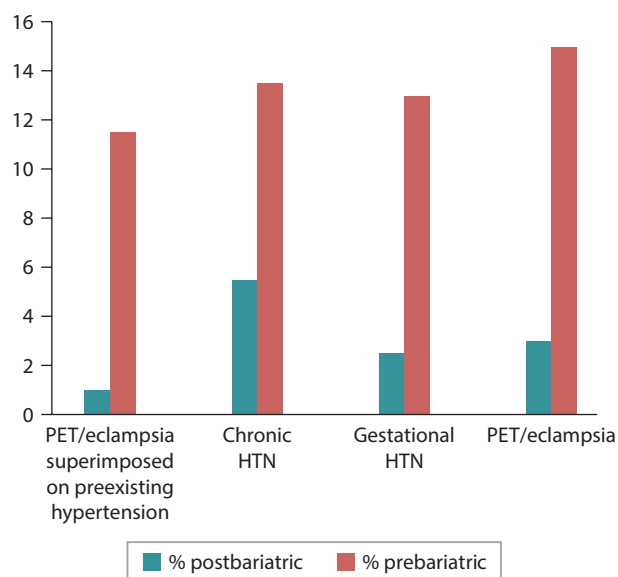


Figure 34.2 The risk for hypertensive disorders. HTN, hypertension; PET, preeclampsia toxemia; PIH, pregnancy-induced hypertension. (Adapted from Bennett, W.L. et al., *Br. Med. J.*, 340, c1662, 2010.)

A potentially major concern is the association between bariatric surgery and NTD. This association was reported in a number of case reports^{127,128} and may be attributed to the biologic plausibility of folate deficiency and hyperhomocysteinemia in postoperative woman.^{121,128} However, Weintraub et al.¹⁰⁷ did not report a higher rate of fetal malformations among 507 deliveries after bariatric surgery as compared to 301 deliveries before bariatric surgery after controlling for maternal age and preterm delivery in a multivariate model.

Reassuring findings were also reported by Sheiner et al. in a large study that examined the risk for congenital malformations in 298 pregnancies after bariatric surgery and 158,912 deliveries in the general obstetrical population. In their study, no significant difference was found between the two groups.¹¹¹ The study was powered enough to conclude that no differences were found.

It is obligatory to be aware for any deficiencies and treat them once detection is made. Although it is not known if women require higher doses of folic acid after weight loss surgery,⁸² patients should be encouraged to take adequate folic acid supplementation (800 mcg daily, or even 5 mg) to decrease the risk along with screening via maternal serum alpha-fetoprotein and ultrasound.

Postbariatric surgery: Fertility

It is well established in literature that obesity can be associated with oligoovulation/anovulation that can reduce fecundity rates. Studies have shown that weight loss (both nonsurgical and surgical) could increase fertility for overweight and obese women.^{11–13} In one series, 15 of 32 women that were unsuccessful at becoming pregnant prior to bariatric surgery became pregnant following surgery.⁷⁵ In another study by Teitelman et al.,¹²⁹ 70 out of 98 anovulatory women regained normal menstrual cycles after surgery, and those who regained ovulation lost significantly more weight than those who remained anovulatory. In a recent retrospective study of 110 obese infertile women who were unsuccessful in their attempts to conceive prior to bariatric surgery, 69 became pregnant after surgical weight loss. The authors found only the amount of weight loss (OR 20.2, $p = 0.001$)

Table 34.6 Summary of selected studies on cesarean delivery rate in pregnancy after bariatric surgery

Study (author, year, country)	Cases	Comparison group	Type of surgery	Main findings
Sheiner et al. ¹¹¹ 2004, Israel	298 deliveries	Pregnancy cohort without BS, $n = 158,912$	BS	Higher rate of CS even after controlling for confounders using logistic regression and Mantel-Haenzel analyses (OR 2.4)
Ducarme et al. ⁹² 2007, France	13 deliveries	414 deliveries in obese women	LAGB	Decreased rate CS among post-LAGB women as compared to obese controls (15.3% vs. 34.4%)
Burke et al. ¹⁰⁸ 2010, USA	354 deliveries	346 presurgical deliveries	BS (87%/75% RYGB)	Women with delivery after BS had lower incidences of CS (28% vs. 43%, OR 0.53)
Weintraub et al. ¹⁰⁷ 2008, Israel	507 deliveries	301 presurgical deliveries	LAGB	Increased risk for CS among postsurgical deliveries (OR 1.9)
Patel et al. ¹⁰² 2008, USA	26 deliveries	254 deliveries stratified by BMI	RYGB	- Higher rate of CS among post-RYGB women as compared to nonobese controls - NS when compared to obese or severely obese controls
Wax et al. ¹⁰³ 2008, USA	38 deliveries	76 deliveries matched for maternal age and prior CS	RYGB	NS

Abbreviations: BS, bariatric surgery; CS, cesarean section; LAGB, laparoscopic adjustable gastric banding; NS, no significant difference was found; OR, odds ratio; RYGB, Roux-en-Y gastric bypass.

Table 34.7 Summary of selected studies on birth weight in pregnancy after bariatric surgery

Study (author, year, country)	Cases	Comparison group	Type of surgery	Main findings
Lesko et al. ¹²⁶ 2012, USA	70 deliveries	140 deliveries matched for presurgical BMI $\pm$ 6	BS (85.7% RYGB)	• Neonates were significantly more likely to be SGA in the BS group (17.4%) than the morbidly obese group (5.0%) (OR 3.94). • The incidence of macrosomia (defined as birth weight more than 4000 g) was lower as compared with control group (OR 0.21).
Sheiner et al. ¹¹¹ 2004, Israel	298 deliveries	Pregnancy cohort without BS, $n = 158,912$	BS	• Higher rate of IUGR (5% vs. 2%) and macrosomia in postsurgical patients as compared to the general population. • IUGR was not significant when confounders were controlled for. • Macrosomia remained significant after control of confounders (OR 2.1).
Ducarme et al. ⁹² 2007, France	13 deliveries	414 deliveries in obese women	LAGB	Decreased rate of SGA (7.7% vs. 10.6%) and macrosomic infants (7.7% vs. 14.6%) post-LAGB as compared to obese controls.
Dixon et al. ⁷⁰ 2005, Australia	79 deliveries	79 deliveries matched for BMI, age, and parity	LAGB	NS
Weintraub et al. ¹⁰⁷ 2008, Israel	507 deliveries	301 presurgical deliveries	LAGB	• Decreased risk for macrosomia after BS as compared to deliveries before surgery. • NS in risk for SGA infants.
Josefsson et al. ¹²⁵ 2011, Sweden	126 deliveries	Pregnancy cohort without BS $n = 188,500$	BS	Women surgically treated before their first child more often delivered SGA infants compared with the children born to the reference mothers (5.6% vs. 2.1%).
Patel et al. ¹⁰² 2008, USA	26 deliveries	254 deliveries stratified by BMI	RYGB	• Decreased rate of macrosomia post-RYGB (0% vs. 18.5%) as compared to severely obese controls. • NS in rate of IUGR.
Wax et al. ¹⁰³ 2008, USA	38 deliveries	76 deliveries matched for maternal age and prior CS	RYGB	NS

Abbreviations: BS, bariatric surgery; CS, cesarean section; IUGR, intrauterine growth restriction; LAGB, laparoscopic adjustable gastric banding; NS, no significant difference was found; OR, odds ratio; RYGB, Roux-en-Y gastric bypass; SGA, small for gestational age.

Table 34.8 Summary of selected studies on birth defects rate in pregnancy after bariatric surgery

Study (author, year, country)	Cases	Comparison group	Type of surgery	Main findings
Sheiner et al. ¹¹¹ 2004, Israel	298 deliveries	Pregnancy cohort without BS, $n = 158,912$	BS	NS
Weintraub et al. ¹⁰⁷ 2008, Israel	507 deliveries	301 presurgical deliveries	LAGB	Increased rate of fetal malformation (OR 2.5) but NS once maternal age and preterm delivery were controlled for
Patel et al. ¹⁰² 2008, USA	26 deliveries	254 deliveries stratified by BMI	RYGB	NS
Wax et al. ¹⁰³ 2008, USA	38 deliveries	76 deliveries matched for maternal age and prior CS	RYGB	NS

Abbreviations: BS, bariatric surgery; CS, cesarean section; LAGB, laparoscopic adjustable gastric banding; NS, no significant difference was found; OR, odds ratio; RYGB, Roux-en-Y gastric bypass.

and the achieved BMI ($p = 0.001$) after surgery were good predictors for successful pregnancy regardless of the type of surgical procedure the woman underwent.¹³⁰

However, in spite of these encouraging data, when compared to nonobese controls, studies have demonstrated inconsistency regarding fertility outcomes as some reports do not demonstrate any significant difference in fertility between normal and postoperative women, while others show slightly worse outcomes.¹⁰⁹ Our group¹¹¹ had found elevated rates of infertility treatments in postbariatric surgery patients as compared to the general population even after controlling for potential confounders such as maternal obesity. Nevertheless, it should be emphasized that infertility treatments may not be a perfect marker for fertility status. Contrary to our prior findings, more recent studies comparing postbariatric patients to obese or preoperative parturients found no significant difference in the rate of infertility treatment before or after surgery.^{29,107}

In conclusion, generally, postsurgical women show increased fertility when compared to obese controls.¹⁰⁹ When compared to nonobese controls, studies have demonstrated inconsistent results. Currently, it is agreed by most experts that bariatric surgery is not the primary treatment for infertility in severely obese women.^{112,131}

Summary of key points

1. Obesity is an epidemic and is considered to be one of the most pressing concerns in the developed world.
2. Close to one-third of women of childbearing age (20–39 years) are classified as obese in the western society, and an additional quarter of women in this age group are overweight, a fact that can eventually lead to adverse consequences for their future reproductive health, pregnancy, and long-term health.
3. Rates of surgical weight loss procedures have increased dramatically over the recent decade as surgery is probably the best treatment for obesity.

4. Postbariatric surgery parturients are becoming a new obstetric group with unique risks and possible fetal and maternal outcomes.
5. Pregnancy after bariatric surgery appears to be generally safer than pregnancy in obese women.
6. Routine nutritional screening, recommendations for appropriate supplements, and monitoring compliance are obligatory for postoperative pregnant women.
7. Life-threatening surgical complications might be nonspecific and could be difficult for obstetricians to recognize. All pregnant women with a history of bariatric surgery with severe abdominal pain should also be examined by a general surgeon.
8. There is no general practical consensus in women post-LAGB to prophylactically deflate the band once pregnancy is detected.
9. Weight gain recommendations are based on IOM guidelines. Caloric restriction during pregnancy is not recommended even at the price of continuing to be overweight.
10. GCT is not well tolerated in patients who have undergone a malabsorptive procedure; alternative screening ways for GDM should be implemented.
11. Severely obese women should be offered bariatric surgery with a sufficient interval before conception to allow weight reduction.
12. More powered studies are needed in order to conclude about optimal surgical-to-conception interval; currently women are advised to avoid conception for 12 months following bariatric surgery.
13. Postoperative patients tend to have either a similar or lower rate of CD compared to obese women who have not undergone bariatric surgery.
14. The risk of obstetrical complications, such as GDM and hypertensive disorders as well as fetal macrosomia, is significantly reduced following bariatric surgery. There is a possible risk for SGA infants.
15. Systematic studies have repeatedly failed to link the history of bariatric surgery with poor perinatal outcome.
16. Generally, postsurgical women show increased fertility when compared to obese controls.

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35 Fetal lung maturity

Gian Carlo Di Renzo, Giulia Babucci, and Graziano Clerici

Introduction

The functional immaturity of lung tissue leads to an acute progressive breathing failure, the so-called respiratory distress syndrome (RDS). RDS includes some common clinical signs such as tachypnea, expiratory grunting, nasal flaring, and costal retractions. It is caused by deficient surfactant production causing decreased lung compliance resulting in hypoxia.^{1–4}

Diabetic pregnancy, and particularly poorly controlled maternal diabetes, represents one of the most important risks for RDS.

Though the perinatal mortality rate in pregnancies complicated by diabetes has declined, conditions such as congenital malformation and perinatal morbidity (prematurity, hypoglycemia, macrosomia, asphyxia, hypocalcemia, hyperbilirubinemia, polycythemia, hyperviscosity, hypertrophic cardiomyopathy, and respiratory distress) are still common problems in newborns as demonstrated by a recent Australian study (Table 35.1).^{5–7}

Despite the significant improvement in neonatal care, the morbidity for respiratory complications such as RDS in the infants born from diabetic mothers is remarkable, as well as the cost of the resulting care.⁸

In this kind of high-risk pregnancy, metabolic (glycemia) control and evaluation of fetal well-being with serial ultrasound scans are crucial in the maternal clinic care.

Moreover, all these aspects are important in planning the site, time, and mode of delivery in order to improve offspring outcome.⁹ Particularly, the time of delivery plays a key role in the improvement of neonatal outcome, and it is related to maternal metabolic control and the evaluation of fetal well-being and fetal lung maturity that must be clearly documented.¹⁰

Until recently, RDS was one of the most common and serious diseases in infants of diabetic mothers. In the 1970s, improved management of diabetic pregnancies resulted in a decline in its incidence from 31% to 3%.¹¹

The observation of Kulovich indicates that nondiabetic fetus achieves pulmonary maturity at a mean gestational age of 34–35 weeks. Interestingly, by 37 completed weeks, 86% of the lecithin/sphingomyelin (L/S) ratio and 68% of the phosphatidylglycerol (PG) values were in the normal range in diabetic pregnant women, and no significant differences were found from the diabetic and nondiabetic groups.^{4,12}

In a diabetic pregnancy, however, it is not advisable to assume that the risk of neonatal RDS is cancelled after 37 weeks. In fact, full-term infants who were admitted to the intensive care unit with respiratory problems were most probably born from mothers with diabetes. This confirms that neonates who are born from mothers who have pregnancy complicated by medical pathologies, especially diabetes, have frequently an outcome complicated by respiratory diseases/morbidities.¹³

Clinical studies were performed to investigate the incidence of respiratory morbidity in term infants hospitalized in NICU to identify risk factors for such admissions. By those studies, results have shown that diabetes and cesarean delivery, frequently related, are the most important risk factors for NICU admission for RDS and other respiratory morbidities.¹³

Infants delivered before 39 weeks were more likely to be admitted to the NICU for respiratory morbidity than those delivered after that limit. This is complicated by the fact that infants born from mothers with diabetes or hypertension were more likely to be delivered prior to 39 weeks and frequently by cesarean section that, *per se*, increases the risk of neonatal respiratory complications compared to infants born from vaginal delivery.¹³

Thus, a correct management of diabetes during pregnancy particularly to reach a good glycemic control in order to reduce the need to intervene at an early stage is critical.

Pathophysiology of fetal lung maturation in diabetic pregnancies

Neonatal pulmonary function of the infants of diabetic mothers is suboptimal compared with infants of nondiabetic women matched for gestational age.¹⁴

The mechanism by which maternal diabetes influences lung development remains unknown. Although the pathophysiologic functions underlying the occurrence of this problem remain unclear, fetal hyperglycemia and/or hyperinsulinemia, reply to variations in maternal blood, are involved in delayed pulmonary maturation influencing pulmonary surfactant biosynthesis.^{14,15}

The loss of function may be due to inadequate production of alveolar surfactant or abnormal lung maturation and function.

The reason for the delay in lung maturation in infants of diabetic mothers has been the subject of several theories.

Table 35.1 SCN/NICU admission of live born babies, by maternal diabetes in pregnancy status, 2005–2007

	Preexisting diabetes		Gestational diabetes mellitus		No diabetes	
	Number	Percent	Number	Percent	Number	Percent
Admitted	2,843	57.5	12,734	31.9	110,546	13.9
Not admitted	2,104	42.5	27,237	68.1	685,907	86.1
Total	4,947	100.0	39,976	100.0	796,628	100.0
<i>Age-standardized rate (percent) (95% confidence interval)</i>						
Admitted	58.2 (57.7–58.7)		31.8 (31.2–32.3)		13.9 (13.5–14.2)	
Not admitted	41.8 (41.4–42.2)		68.2 (67.4–69.0)		86.1 (85.2–87.0)	
<i>Source:</i> AIHW analysis of NPDC data, Diabetes in pregnancy: Its impact on Australian women and their babies. Copyright Australian Institute of Health and Welfare 2010. This publication is part of the Australian Institute of Health and Welfare’s Diabetes Series. A complete list of the Institute’s publications is available from the Institute’s website: www.aihw.gov.au .						

Some authors have reported irregular production in phospholipids as shown by delayed appearance of PG and the early appearance of phosphatidylinositol (PI). Others have suggested that insulin interferes with the regular timing of lung maturation induced by glucocorticoids, while some others have suggested that the delay in maturation is the result of poor glycemic control regardless of class of diabetes.^{4,16–18}

In vitro studies have largely documented that insulin can interfere with substrate availability for surfactant biosynthesis. Smith et al.¹⁹ demonstrated that, when insulin was added in the presence of cortisol to fetal lung cell cultures, steroid-enhanced lecithin synthesis was abolished. Engle et al.¹⁴ found that higher levels of insulin resulted in declined glucose and choline uptake by fetal rat type II alveolar cells.

However, from other animal studies, it appears that altered expression factors or growth factors may have an important regulatory influence. Particularly, the role of the epidermal growth factor (EGF) in the development of fetal rat lung in the case of maternal diabetes was examined. In order to evaluate the possible role of glucose for the expression of EGF and the growth of the pulmonary tissue, they performed in vitro studies with organotypic cultures of fetal alveolar cells derived from control rats. The results also indicate that glucose has a role in the expression of EGF and that cells exposed to high glucose concentrations are less responsive to EGF probably due to decreased thymidine incorporation.²⁰

Carlson et al. have shown that insulin blocks cortisol action at the level of the fibroblasts by reducing the production of the fibroblast-pneumocyte factor.²¹

Some authors²² reported abnormal timing of phospholipid production in diabetic pregnancy, as indicated by a delay in the appearance of PG in the amniotic fluid only in class A (white) of diabetic pregnancies. Smith²³ postulated that insulin interferes with the normal timing of glucocorticoid-induced pulmonary maturation in the fetus.

Some investigators have disagreed with these findings, reporting that fetal lung maturation occurred later

in pregnancies with poor glycemic control regardless of the class of diabetes.^{24–28}

Bourbon et al. proposed that elevated maternal plasma level of myoinositol in diabetic women may inhibit or delay the production of PG in their fetuses.²⁹

In a recent study of lung histogenesis during intrauterine development of diabetic Sprague Dawley rats at 18, 19, and 21 days of gestation, a delay in alveolarization in the diabetic group was observed, which was confirmed by transmission electron microscopy. In the diabetic group, a small quantity of protein D (associated with surfactant) was detected. The same fetuses, of the diabetic group, presented a delay in lung histogenesis and in the differentiation of type II pneumocytes.³⁰

It is suspected that neonatal respiratory problems in these infants have also a histologic basis in addition to biochemical origin. Previously, Pinter³¹ demonstrated a decreased fluid clearance and lack of thinning of the lung's connective tissue compared with controls in the fetal lung of diabetic rats. Bhavnan³² reported higher lung glycogen levels and reduced pulmonary compliance in offsprings of diabetic rabbits compared with controls.

It is well known that glucose balance has an effect on the incidence of the hyaline membrane disease (Figure 35.1). Several studies have attempted to explain the mechanism of hyaline membrane disease. Hawdon and Aynsley-Green,³³ in an investigation of type II pneumocytes in rats and rabbits, have shown that insulin inhibits the cortisol-dependent production of phosphatidylcholine, apparently as a consequence of the inhibited production of one of the precursors of phosphatidylcholine, fibroblast-pneumocyte factor. In rats, high glucose levels block the transformation of choline to phosphatidylcholine, and butyrate blocks the translation of mRNA into surfactant proteins.

In a demonstration of the central role of glucose homeostasis and decreased insulin resistance in the prevention of gestational diabetes and/or improvement of its outcome, recent studies have used an insulin sensitizer to be administered to pregnant women. In these recent studies, 2 mg of

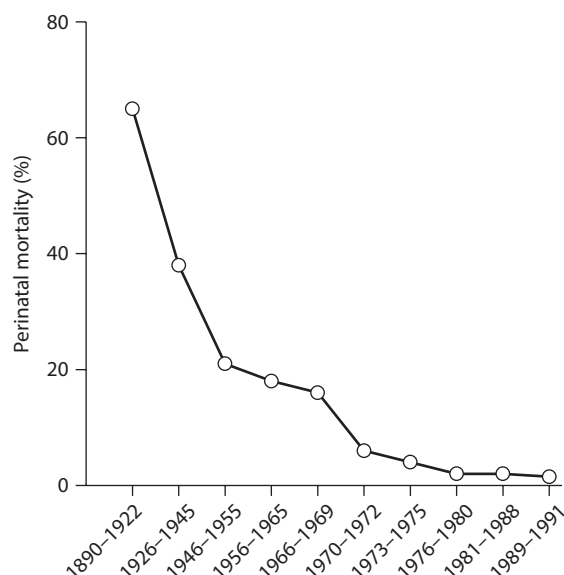


Figure 35.1 Perinatal mortality after introduction of insulin therapy and amniotic fluid analysis. (Modified from Moore, T.R., Diabetes in pregnancy, in: Creasy, R.K. and Resnik, R., eds., *Maternal Fetal Medicine*, 4th ed., Saunders, Philadelphia, PA, 1999, pp. 964–995; Croze, M.L. and Soulage, C.O., *Biochimie*, 95(10), 1811, 2013.)

myoinositol is administered to pregnant women in conjunction with the classic 200 µg of folic acid and only 400 µg of folic acid in the control group.

The results showed a significant reduction in the incidence of gestational diabetes in the group to which myoinositol was administered or at least a more adequate glycemic control in the case of pregnant women who develop gestational diabetes. The available data provide enough evidence for implementing a large-scale, high-quality randomized controlled trial (RCT) looking at the efficacy of inositol in the prevention of GDM in high-risk women.^{34–37}

Evaluation of fetal lung maturity

Fetal lung maturity assessment has become a very important tool in the management of high-risk pregnancies, especially the diabetic ones. The evaluation of the ratio between lecithin and sphingomyelin and the amount of the PG by amniocentesis in the amniotic fluid is the method most widely used to identify fetal lung maturity. Particularly, the evidence of L/S above 2.5 and the presence of PG should be used to predict fetal lung maturity.³⁵

Moreover, amniocentesis in the third trimester is not associated with increased risk of procedure-related complications.³⁶ About 10 mL of amniotic fluid should be collected and analyzed.

In the past, elective preterm delivery for diabetic pregnancies was common in order to avoid unexpected intrauterine death, which is one of the most important complications of gestational diabetes. This practice often resulted in high incidence of neonatal morbidity and mortality. With the improvement of glycemic control (target values blood glucose 3.5 and

5.9 mmol/L and 1 hour postprandial below 7.8 mmol/L), serial ultrasound scans to monitor fetal growth (to prevent fetal macrosomia), and better techniques of antepartum surveillance, the need to perform preterm delivery has decreased. In fact, pregnant women with diabetes who have normal fetal growth and good glycemic control should be waiting for spontaneous labor; on the contrary, in cases of poor metabolic control and/or with evident fetal macrosomia, they can be offered elective birth preferably not before 38 completed weeks.³

Considering the risks of delayed lung maturity in fetuses of diabetic mothers, the assessment of fetal lung maturity is mandatory in the case of very poor metabolic control in diabetes and pregnancy with uncertain date.^{37–40}

Poorly controlled diabetes is one of the conditions that recommends performing amniocentesis, during the third trimester of pregnancy, in order to analyze amniotic fluid composition that reflects the status of the fetal lung.

A number of diagnostic methods with a high degree of accuracy have been developed and are now available.

Phospholipids

The L/S ratio was introduced by Gluck and colleagues in 1971.⁴¹ The test depends on the flow of fetal lung fluid into the amniotic fluid changing its phospholipid composition. The result is expressed as the ratio of lecithin (phosphatidylcholine) to sphingomyelin.

Sphingomyelin is a general membrane lipid and is not related to lung maturational events. The sphingomyelin content in the amniotic fluid tends to fall from about 32 weeks gestational age to term, whereas the more saturated lecithin concentration (a large part from the fetal lung) increases.

The L/S ratio for normal pregnancies is less than 0.5 at 20 weeks, gradually increasing to 1.0 at 32 weeks and around 35 weeks achieving a value of 2.0 correlating it with fetal lung maturity; empirically RDS is unlikely if the ratio is more than 2.0 (Figures 35.2 and 35.3).

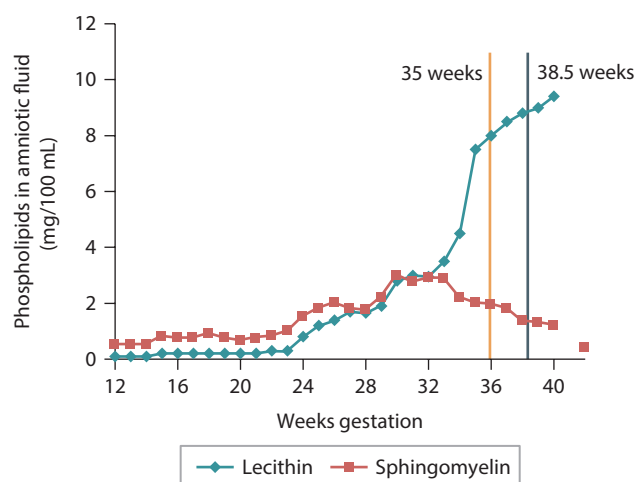


Figure 35.2 Changes in the concentrations of lecithin and sphingomyelin in the amniotic fluid. The vertical lines indicate achieved pulmonary maturity in nondiabetic (black) and diabetic (red) pregnancy.

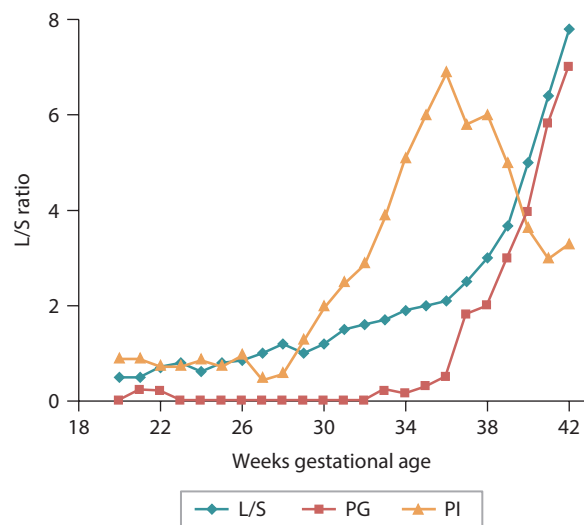


Figure 35.3 Lecithin/sphingomyelin ratio, phosphatidylglycerol, and phosphatidylinositol in the amniotic fluid from normal pregnancies. (Data from Gluck, L. et al., *Am. J. Obstet. Gynecol.*, 120, 142, 1974; De Luca, A.K. et al., *Acta Obstet. Gynecol.*, 88, 1036, 2009; Hallman, M. et al., *Am. J. Obstet. Gynecol.*, 125, 613, 1976; Piper, J.M., *Semin. Perinatol.*, 26, 206, 2002.)

The evaluation of the L/S ratio by chromatography is the standard and reliable method with sensitivity of 83%–97% and specificity of 98%.^{44,45} Nevertheless, chromatography is a challenging test for routine activity because it is complicated to perform and requires special laboratory tools.

Many factors can influence the L/S ratio. Lecithin is found in many body fluids including blood, vaginal secretions, and gastrointestinal fluid.

The value of L/S ratio has been questioned in diabetic pregnancies where there is an increase of false-negative rate that could range from 3% to 27%. Most studies, however, report a low incidence of RDS with an L/S ratio >2.⁴⁶

Some authors show that L/S ratio may not be a reliable indicator of pulmonary maturity in diabetic pregnancies. Those authors affirm that even a ratio above 2.0 does not guarantee lung maturation.^{47,48} Diabetes may affect the secretion of the fetal lung fluid, resulting in a higher removal of phospholipids from the alveolar lining and in an increase false-negative rate.⁴⁸

Other authors noted no difference between diabetic patients and controls.⁴⁹ When maternal diabetes is well controlled during pregnancy, the L/S ratio can be used to establish the risk of neonatal RDS.⁴⁹

Surfactant of mature lung contains PG, which is absent early in gestation and only appears at about 35 weeks of pregnancy.⁴³

PG is virtually present only in the lung tissue and surfactant. Thus, amniotic fluid contaminated with blood or meconium can be analyzed for this substance.⁵⁰

When PG is present, RDS does not occur except possibly in the case of intrapartum acidemia and hypoxemia. With trace amounts of PG in amniotic fluid, an incidence of RDS <1% has been reported.⁴⁹

Many authors confirmed that the added evaluation of the PG decreases the rate of false positives significantly and improves the specificity of the L/S ratio.⁴⁹

The appearance of the acidic phospholipid PG may be delayed by fetal hyperinsulinemia, and this delay is associated with an increased incidence of RDS. In fact, the appearance of PG has been reported to be delayed in pregnancies of diabetic women and, for that, remains a reliable predictor of pulmonary maturity. However, the absence of PG in diabetic pregnancy does not assume the diagnosis of pulmonary immaturity, since PG fails to appear in 10% of amniotic fluid samples by 40 weeks gestation and the presence of PG is reported in only 47% of samples studied for both diabetic and nondiabetic patients with mature L/S ratios and gestation of 34 weeks or beyond.⁴⁹

Prior to lung maturation, there is a progressive increase of PI in the amniotic fluid particularly from 26 to 33–35 weeks. PG appears in the amniotic fluid as the percentage of PI begins its decline.⁴³ The “lung profile” is a test that combines the L/S ratio with measurements of the percentage of disaturated (acetone precipitable) lecithin (phosphatidylcholine), PI, and PG in the amniotic fluid.²² The information provided by this profile enhances the accuracy of diagnosing fetal lung maturity and gives further information on lung development. In a small group of cases, the specificity increased from 69% to 93% by substituting the lung profile for the L/S ratio.¹¹

The introduction of the immunological (Amniostat-FLM) evaluation of PG provides rapid result with minimal equipment necessary. This method has a false-positive rate >50%. Nevertheless, literature data confirm the utility of this approach as a screening test for their rapidity and simplicity of execution, particularly for specificity in the case of contamination and/or diabetic patients.

The results of PG assay by thin-layer chromatography and Amniostat-FLM were reported to be concordant in 90%–95% of the cases.⁴⁹

Proteins

The predominant protein involved in surfactant metabolism is a 35 kDa protein, called surfactant-associated protein 35 (SAP-35). This protein originates from the type II alveolar cells. An increase in the level of this protein in the amniotic fluid occurs near term, and a significant correlation with pulmonary maturity has been described.^{51,52} The measurement of this protein is simply available using ELISA method and monoclonal antibodies. For Hallman et al., the test can predict RDS with an accuracy similar to that of L/S ratio.⁵² In high-risk pregnancies such as diabetes or hypertension, the levels of SAP-35 have lower correlation with fetal lung maturity and are probably not reliable in these situations.⁵²

Lipids

Cholesterol palmitate is present in the amniotic fluid at term. Its role is unknown, but it could be involved in the transport of palmitic acid that is used in the synthesis of saturated phosphatidylcholine. Thin-layer chromatography and densitometry are reported as simple methods for determining

this substance in the amniotic fluid.⁵³ It was observed that levels of cholesterol palmitate were correlated with fetal lung maturity; on the contrary, a similar correlation was not demonstrated in diabetic pregnancies.⁵⁴

Fluorescence polarization

There are two main systems used to measure fluorescent polarization: the Fetal lung maturity analyzer (FELMA) microviscometer and the Tdx system. The fluorescent polarization of amniotic fluid is in large part determined by binding of the probe to phospholipid structures and to the albumin as a predominant protein.⁵⁵ Fluorescence polarization of the amniotic fluid is inversely related to the L/S ratio.^{56,57} The specificity of this method to predict RDS ranges from 50% to 70%.^{58,59} The technique is not reliable when the amniotic fluid is contaminated with blood or meconium. Maternal diabetes may have variable effects on the fluorescent polarization values, and in this condition, this method is an unreliable indicator of fetal lung maturity.⁶⁰

Comparing current techniques

Several recent studies have examined the capacity of the various tests in today's use for predicting neonatal lung maturity.^{9,61} Lamellar bodies (LB)—1 to 5 μm lamellated structures synthesized by type 2 granular pneumocytes—can be counted using commercial blood cell analyzers.⁶² These storage granules contain phospholipids, cholesterol, and several surfactant-specific proteins that become pulmonary surfactant. The first appearance of lamellar bodies in the cytoplasm of fetal pneumocytes is between 20 and 24 weeks of gestation⁶³; the lamellar bodies become more numerous and larger and are secreted into fetal alveoli; and fetal breathing movements and exudation of lung fluid carry these lamellar bodies into the amniotic fluid. The phospholipid content and the laminated structure change when the fetal lung is mature. The measure of the surfactant/albumin ratio in the amniotic fluid represents the fetal lung maturity test. Other means of predicting the maturity include calculating the L/S ratio, measuring the amniotic fluid level of PG,⁶⁴ performing the foam stability test⁶⁵ or a fluorescence polarization assay,⁶⁶ and measuring amniotic fluid optical density at 650 nm.⁶⁷ All these tests measure some aspects of the pulmonary surfactant contained in the amniotic fluid, and none is perfect for the prediction of lung maturity. The ideal test must be readily available and cheap with good predictive value. Abd El Aal et al. with an important study found that a lamellar body count is a good screening test for predicting neonatal lung maturity. It is comparable to the fetal lung maturity assay by fluorescence polarization and better in others.

Summary

To date, the method most widely used to assess the fetal lung maturity is the evaluation of the L/S ratio and PG. Particular attention should be given to macrosomia, as

the mirror of a bad maternal glycemic control, and/or an uncertain dating of pregnancy.

Caution should be used in planning the time of delivery of patients with a mature L/S ratio and absent PG. The L/S ratio can be used to assess fetal lung maturity when glucose levels have been well controlled in a diabetic pregnancy. When control has been unreliable or is difficult to assess, positive PG or higher L/S ratio (>2.5) should be used to predict fetal lung maturity.³⁴

Ghidini et al.⁶⁸ suggest that an L/S ratio of ≥ 3.0 represented the optimal trade-off between sensitivity (68%) and false-positive rate (6%) in the prediction of the presence of PG. Similarly, a significant relationship exists between LB count values and the presence of PG. An LB count of $\geq 50,000$ represents the optimal trade-off between sensitivity (92%) and false-positive rate (0%) in the prediction of the presence of PG.

The presence of PG or an L/S ratio of ≥ 2.5 indicates that the fetal lungs are mature. The confirmation of fetal lung maturity should be obtained and used to plan the time of delivery.

However, it is still unclear if there is a delay in fetal lung maturation between diabetic and nondiabetic pregnant women at the same period of gestation. Some studies have confirmed a delay in pregnant women with diabetes, while other studies have not demonstrated a significant difference in fetal lung maturity in pregnant women with diabetes compared with the nondiabetic.⁴

Furthermore, it is still a matter of debate if preexisting diabetes has a role in the delay of fetal lung maturation⁴ (Figure 35.4). Also, Di Renzo et al. in a study published in 2011 investigated for the assessment of lung maturity. In the study, conducted between 2008 and 2010, 105 cases of gestational diabetes were found that were assessed for fetal lung maturity by evaluating the L/S ratio and the presence of PG considering an L/S ratio of >4 and PG present at gestational age between 36 and 40 weeks. The vast majority was found

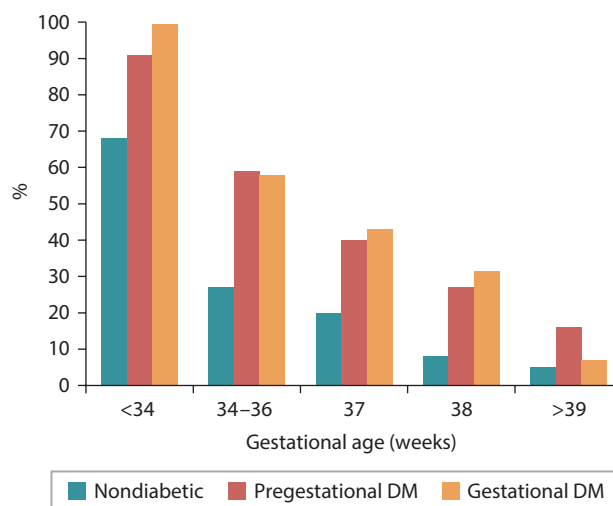


Figure 35.4 The controversy surrounding fetal lung maturity in diabetic pregnancy: a reevaluation. (From Langer, O., J. *Matern. Neonatal. Med.*, 12, 428, 2002. With permission.)

Table 35.2 Assessment of lung maturity: Results

77 mature
 28 not mature (14 of them >38 weeks)
 10 retreatment with corticosteroids
 13 repeated after 3–5 days
 11 mature
 2 RDS

Source: Di Renzo et al. (2011), unpublished data.

to have reached the fetal lung maturity, but a substantial minority (28 cases) was immature, half of which were found to be at an age higher than 38 weeks of gestation. In the immature cases, readministering corticosteroid has been necessary in giving a final result, however, of two cases of RDS at birth (Table 35.2).⁶⁹

Induction of fetal lung maturity

When fetal lungs are immature, the infant will develop RDS. About 25% of untreated ones die within 28 days of birth, and another 25% will develop chronic lung disease.

Since 1972, when it was reported a decreased incidence of RDS in newborn from a mother who received a prenatal administration of corticosteroids,⁶⁹ several randomized trials about the role of steroids (and other drugs) to induce and/or improve pulmonary maturity have been conducted. Many reports have confirmed the original findings that antenatal administration of glucocorticoids to the mother is associated with a statistically significant reduction in the incidence of RDS.^{70,71}

Almost all have demonstrated the efficacy of corticosteroid treatment in reducing perinatal morbidity and mortality, as confirmed by an RCT that has compared a single course of corticosteroids with either placebo or no intervention, confirming the efficacy of this treatment.⁷²

During the last decade, the strategy for the prevention of RDS has been directed toward the acceleration of fetal lung maturity by administering various hormones to the mother, but at the present time, glucocorticoids remain the most widely used agents.

Glucocorticoids act in different ways on the maturation process,⁷³ known already for many years, as listed in Table 35.3.

The main institutions have been producing and updating recommendations and guidelines on the use of antenatal corticosteroids (ACSs):

- The National Institutes of Health (NIH) published a Consensus Development Conference Statement in 1994 on the use of ACSs⁷⁴ and in 2000 a revision to the use of repeated courses of ACS.⁷⁵
- In 2011, the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice^{76,77} whose conclusions were in agreement with NIH.

Table 35.3 Actions of glucocorticosteroids

Prenatal administration significantly increases content of elastin in the fetal lung.
 As transcriptional activators for the synthesis of surfactant-associated proteins (SP-A and SP-B).
 On lung fibroblasts that elaborate fibroblast pneumocyte factor that subsequently acts on type II cells and stimulates surfactant synthesis.
 Prenatal administration makes the immature lung more responsive to exogenous surfactant.
 Stimulate upregulation of corticotropin releasing hormone (CRH) output by the placenta.

- The Royal College of Obstetricians and Gynaecologists (RCOG)^{78,79} published the fourth edition of their guideline in October 2010.

In the last few years, new important information about ACS to consider different unresolved topic issues has been published: fetal, neonatal, and maternal effects of ACS, single versus multiple courses of ACS therapy, characteristics optimal steroids, the ideal dose, and the route of administration.⁷¹

Concerning the long-term effects on the use of multiple steroid treatments in the last Cochrane Review (2006), Roberts and Dalziel have demonstrated that ACS does not improve the risk, to the mother, of death, chorioamnionitis, or puerperal sepsis.⁷²

Asztalos suggested that ACS reduces birth weight that is associated with adverse adult outcomes like stroke, hypertension, coronary heart disease, and type 2 diabetes. In animal studies, the long-term effects of ACS exposure on hypothalamic–pituitary–adrenal (HPA) axis activity and neurological function are largely documented. From that, it appears that ACS, regardless of dose exposure, can affect the fetal development of the HPA axis causing permanent changes in this axis that persists through life and manifested itself by chronic illness and behavioral changes.^{80–83}

The possible long-term consequences of AGC exposure in HPA axis function and subtler neurodevelopmental outcomes, including adaptation to stress, cognition, behavior, and the cardiovascular and immune responses, are confirmed by another study of Waffarn and Davis.⁸⁴ Further information is required concerning the long-term effects into adulthood.

In consideration of the effectiveness of ACS to reduce RDS and other complications, the guideline recommended the use of ACS in all women with a high risk of preterm delivery (24–34 weeks) and after 34 weeks gestation only if there is an evidence of pulmonary immaturity, particularly in patients with conditions that cause a delay in the fetal lung maturation as diabetes.⁷¹

Considering the choice of the type, dose, and mode of corticosteroid administration, today, betamethasone, as the steroid of choice, is recommended to be given in a course of two doses of 12 mg administered intramuscularly 24 hours apart⁷⁹ (Table 35.4). Recent evidences appear to support the

Table 35.4 Guidelines of the Royal College of Obstetricians and Gynaecologists: Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality

This is the fourth edition of this guideline, which was previously published in April 1996, December 1999 and February 2004. The previous guideline was entitled *Antenatal Corticosteroids to Prevent Respiratory Distress Syndrome*.

1. Purpose and scope

The aim of this guideline is to provide up-to-date information on the appropriate use of antenatal corticosteroid therapy in women whose babies are at risk of complications owing to either preterm birth or elective cesarean section at term.

This guideline does not assess the effectiveness of tests in the prediction of preterm delivery (e.g., ultrasound scanning for cervical length, cervical fibronectin measurement) or other interventions that may prevent preterm labour (e.g., tocolysis).

2. Background

There is evidence to suggest that antenatal corticosteroids are effective not only in reducing respiratory distress syndrome (RDS) but also in reducing other complications of prematurity such as intraventricular haemorrhage (IVH). The title of this guideline has been changed to Antenatal Corticosteroids to Prevent Neonatal Morbidity and Mortality to include all groups of women and all outcomes.

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Greentop Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews), DARE, Embase, TRIP, Medline and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews and meta-analyses and cohort studies. The search was restricted to articles published between 2002 to July 2008. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search words included 'steroids', 'premature labour', 'premature fetus' and 'membrane rupture', and the search was limited to humans and to the English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews.

4. What are the benefits of antenatal corticosteroids?

Antenatal steroids are associated with a significant reduction in rates of neonatal death, RDS and intraventricular haemorrhage and are safe for the mother.

Antenatal corticosteroids have no known benefits for the mother.

A Cochrane review of 21 studies (3885 women and 4269 infants) showed that treatment of women at risk of preterm birth with a single course of antenatal corticosteroids reduced the risk of neonatal death by 31% (95% CI 19–42%), RDS by 44% (95% CI 31–57%) and intraventricular haemorrhage by 46% (95% CI 31–67%).¹ Antenatal corticosteroid use is also associated with a reduction in necrotising enterocolitis, respiratory support, intensive care admissions and systemic infections in the first 48 hours of life compared with no treatment or treatment with placebo.

5. At what gestation should antenatal steroids be used?

Clinicians should offer a single course of antenatal corticosteroids to women between 24+0 and 34+6 weeks of gestation who are at risk of preterm birth.

Antenatal corticosteroids can be considered for women between 23+0 and 23+6 weeks of gestation who are at risk of preterm birth.

The decision to administer corticosteroids at gestations less than 24+0 weeks should be made at a senior level taking all clinical aspects into consideration.

The data are strongest for gestations between 26+0 and 34+6 weeks. The data for pregnancies between 24+0 and 26+0 weeks of gestation are scarce, with only one trial (49 infants) contributing data to the Cochrane review.¹

The conclusion of the authors of the Cochrane review¹ and the American Congress of Obstetricians and Gynecologists (ACOG) Committee opinion (2008)² is that, despite the paucity of data at earlier gestations, the reduction in outcomes other than RDS at 26+0 weeks of gestation would suggest that there is some benefit in corticosteroid prophylaxis at earlier gestations between 24+0 and 26+0 weeks.

In a prospective cohort of 4446 infants between 22+0 and 25+0 weeks of gestation, multivariable analyses showed that those who received intensive care, were exposed to antenatal corticosteroids, were of female sex, were from singleton pregnancies, and of higher birth weight (per each 100 g increment) had a reduced risk of death. Among survivors, the risk of death, or profound or any neurodevelopmental impairment at 18–22 months corrected age, was reduced.³ These reductions were similar to those associated with a 1-week increase in gestational age.

A retrospective cohort study on 181 infants born at 23 weeks of gestation revealed that those exposed to antenatal corticosteroids had decreased odds of death (OR 0.32, 95% CI 0.12–0.84), with no significant differences in the occurrence of necrotising enterocolitis among survivors (15.4% compared with 28.6%, $P = 0.59$) or severe intraventricular haemorrhage (23.1% compared with 57.1%, $P = 0.17$). Only a complete course of corticosteroids was associated with a decreased odds of death (OR 0.18, 95% CI 0.06–0.54).⁴ The study concluded that neonates at 23 weeks of gestation whose mothers completed a course of antenatal corticosteroids had an associated 82% reduction in odds of death.

Evidence from the EPICure study, a prospective cohort study, showed that of 283 babies born at less than 26+0 weeks of gestation assessed at 2.5 years and 241 assessed at 6 years, antenatal corticosteroids was associated with an increased mental development index.⁵

(Continued)

Table 35.4 (Continued) Guidelines of the Royal College of Obstetricians and Gynaecologists: Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality

Trial data are scanty for pregnancies at the extreme of prematurity. Obstetricians currently have the discretion to administer steroids before the 24th week of pregnancy, but the whole clinical picture needs to be taken into account with respect to intact survival data as well as the chance of any survival based on antenatal assessment of viability at these extremes (e.g., by estimation of fetal weight). In this context, we have advised caution and discussion at senior level prior to considering antenatal corticosteroid administration at 23+0 to 23+6 weeks of gestation.

6. How long after administration is a course of antenatal corticosteroids most effective?

Antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver 24 hours after and up to 7 days after administration of the second dose of antenatal corticosteroids.

Antenatal corticosteroid use reduces neonatal death within the first 24 hours and therefore should still be given even if delivery is expected within this time.

Reduction in RDS is seen in infants born up to 7 days after the first dose (RR 0.46, 95% CI 0.35–0.60, nine studies, 1110 infants).¹ No reduction in neonatal death, RDS or cerebro-ventricular haemorrhage is seen in infants delivered more than 7 days after treatment with antenatal corticosteroids.¹

Antenatal corticosteroid use reduces neonatal death even when infants are born less than 24 hours after the first dose has been given (RR 0.53, 95% CI 0.29–0.96, four studies, 295 infants).¹

However, caution should be exercised in the interpretation of the data. The question as to whether the effects of antenatal corticosteroids change with time to delivery cannot be answered by existing analyses, the main reason being that the time periods chosen for subgroup analysis were arbitrary. All the babies born at term were in one subgroup. Analyses based on subgroups defined by outcomes not known at randomisation are subject to considerable bias. This question would require re-analysis of individual patient data to clarify whether the association is real.

7. How safe is the use of antenatal corticosteroids?

Women may be advised that the use of a single course of antenatal corticosteroids does not appear to be associated with any significant short-term maternal or fetal adverse effects.

Evidence on the longer-term benefits and risks of a single course of antenatal corticosteroids shows no clear difference in adverse neurological or cognitive effects. There is still insufficient evidence on the longer-term benefits and risks of multiple courses of antenatal corticosteroids.

Studies in the sheep model have shown that injections with glucocorticoids enhance fetal lung maturation but are associated with developmental and other functional alterations that are of concern. Weekly doses to the sheep mother are associated with restricted fetal growth, delayed myelination of the central nervous system, altered blood pressure soon after birth and increased insulin response to glucose challenge in early adulthood.

There have therefore been concerns about whether steroid administration may have adverse effects on the long-term outcomes of children exposed in the antenatal period. Multivariate analyses in humans have shown that increasing the number of glucocorticoid exposures, for the purpose of enhancing lung maturation prior to preterm birth, is associated with reduced birth weight and behavioural disorders at 3 years of age.⁷

The Cochrane review and other studies have shown that a single course of corticosteroid therapy for preterm birth results in benefit without causing significant adverse effects such as neonatal or maternal sepsis.^{1,8,9} The Cochrane review revealed that no statistically significant differences were seen for chorioamnionitis (RR 0.91, 95% CI 0.70–1.18, 12 studies, 2485 women) or puerperal sepsis (RR 1.35, 95% CI 0.93–1.95, eight studies, 1003 women). There were no maternal deaths, but the randomised controlled trials were underpowered to detect such a difference (RR 0.98, 95% CI 0.06–15.50, three studies, 365 women).¹

Long-term follow-up of survivors from randomised trials of antenatal corticosteroid therapy through childhood to adulthood (up to 20 years of age) shows no clear adverse neurological or cognitive effects.^{10,11}

A randomised controlled trial showed that children who had been exposed to repeat as compared with single courses of antenatal corticosteroids did not differ significantly in physical or neurocognitive measures. However, there was a nonsignificant higher risk of cerebral palsy among children who had been exposed to repeat doses of corticosteroids (RR 5.7, 95% CI 0.7–46.7, $P = 0.12$). The number of children with cerebral palsy was small. This was, however, felt to be of concern and warranting further study.¹²

Furthermore, studies on long-term cardiovascular risks, cognitive functioning, working memory and attention, psychiatric morbidity, handedness or health-related quality of life on the survivors of the first and largest double-blind, placebo-controlled, randomised trial of a single course of antenatal betamethasone for the prevention of neonatal RDS at age 31 found no differences between groups exposed to betamethasone and placebo.

8. Are there any contraindications to the use of antenatal corticosteroids?

Caution should be exercised when giving corticosteroid therapy to women with systemic infection including tuberculosis or sepsis. Corticosteroids suppress the immune system, so there is a risk that their use may activate latent infections or exacerbate fungal infections. In a woman with systemic infection, it may theoretically suppress the immune response to infection. There is no evidence to suggest that a single course of corticosteroids would have a profound effect in women with systemic infection, but caution should be exercised in its use.

Senior opinion should be sought when contemplating delaying delivery for steroid prophylaxis in cases of overt chorioamnionitis.

(Continued)

Table 35.4 (Continued) Guidelines of the Royal College of Obstetricians and Gynaecologists: Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality

A large meta-analysis of observational studies reports that clinical chorioamnionitis is significantly associated with both cystic periventricular leukomalacia (RR 2.6, 95% CI 1.7–3.9) and cerebral palsy (RR, 1.9, 95% CI 1.5–2.5).^{15,16} This would suggest that with chorioamnionitis, a course of antenatal corticosteroids may be started, but should not delay delivery if indicated by maternal or fetal condition.

9. Who should receive antenatal corticosteroids?

Antenatal corticosteroids should be given to all women at risk of iatrogenic or spontaneous preterm birth up to 34+6 weeks of gestation.

Antenatal corticosteroids should be given to all women for whom an elective cesarean section is planned prior to 38+6 weeks of gestation.

There is no evidence to support a practice of prophylactic steroids in women with a previous history of preterm delivery or multiple pregnancy who show no signs of being at risk of iatrogenic or spontaneous preterm birth.

There is evidence of benefit in all major subgroups of preterm babies, such as women with premature rupture of membranes and pregnancy-related hypertension syndromes as well as the subgroups discussed below.¹ This benefit is irrespective of race or gender. A single course of antenatal corticosteroids should be considered routine for preterm delivery with few exceptions.

9.2 In women with diabetes mellitus

Diabetes mellitus is not a contraindication to antenatal corticosteroid treatment for fetal lung maturation.

Women with impaired glucose tolerance or diabetes who are receiving fetal steroids should have additional insulin according to an agreed protocol and be closely monitored.

Women with either insulin-dependent diabetes or gestational diabetes were not entered into randomized controlled trials of antenatal corticosteroid therapy. There is therefore no evidence from randomized controlled trials that antenatal corticosteroid therapy is either safe or effective in these circumstances. Maternal hyperglycemia can adversely affect fetal lung maturity. It is possible that any benefit of corticosteroids could be offset by corticosteroid-induced hyperglycemia.¹⁹

However, the National Institute of Health and Clinical Excellence (NICE) has published a clinical guideline for diabetes in pregnancy that states that 'diabetes should not be considered a contraindication to antenatal corticosteroids'.²⁰ The NICE guideline recommends that diabetic women receiving steroids should have additional insulin according to an agreed protocol.

10. What is the best dose and route of administration for a course of antenatal corticosteroids?

Betamethasone 12 mg given intramuscularly in two doses or dexamethasone 6 mg given intramuscularly in four doses are the steroids of choice to enhance lung maturation.

The most extensively studied regimens of corticosteroid treatment for the prevention of RDS are two doses of betamethasone 12 mg given intramuscularly 24 hours apart or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart. Evidence for other dosing regimens such as the commonly used two doses of betamethasone 12 mg given 12 hours apart is sparse (two trials, 92 women),^{29,30} but it would seem reasonable that as long as 24 mg of either drug is given within a 24–48-hour period, any dosing regimen can be used.

A large nonrandomised retrospective study has suggested that infants exposed to antenatal betamethasone have less neonatal cystic periventricular leukomalacia than infants exposed to antenatal dexamethasone.³¹ Another historical cohort study used multivariate logistic regression analysis to compare the two steroid-treated groups with each other. It showed the risk of neonatal death was lower with betamethasone than with dexamethasone (OR 0.44 for betamethasone versus 0.73 with dexamethasone, $p < 0.05$).³²

The Cochrane review on antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth suggests that betamethasone treatment causes a larger reduction in RDS than dexamethasone. Since then, in a Cochrane review on different corticosteroid regimens (ten trials, 1089 women and 1161 infants), dexamethasone decreased the incidence of intraventricular haemorrhage compared with betamethasone (RR 0.44, 95% CI 0.21–0.92, four trials, 549 infants).³³

This review advised caution in suggesting benefit of dexamethasone over betamethasone. A randomised controlled trial looking at long-term outcomes in children treated with dexamethasone would be required as this form of corticosteroid has not been studied in the long term. For current practice, the use of either corticosteroid is acceptable.

Comparison of oral versus intramuscular administration of dexamethasone (one trial, 183 infants) suggests that oral administration increased the incidence of neonatal sepsis (RR 8.48, 95% CI 1.11–64.93) in one trial of 183 infants. No statistically significant differences were seen for other outcomes reported. The authors suggest that very few conclusions about the optimum regimens can be made.

11. When should an antenatal course of corticosteroids be repeated?

Weekly repeat courses of antenatal corticosteroids reduce the occurrence and severity of neonatal respiratory disease, but the short-term benefits are associated with a reduction in weight and head circumference. Weekly repeat courses are not recommended.

A single rescue course may be considered with caution in pregnancies where the initial course was given at less than 26+0 weeks of gestation. Senior opinion should be sought if a rescue course is to be considered.

(Continued)

Table 35.4 (Continued) Guidelines of the Royal College of Obstetricians and Gynaecologists: Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality

Animal studies and observational studies in humans have suggested that multiple courses of steroids may lead to possible harmful effects including growth delay, brain developmental delay, lung development problems, necrotising enterocolitis, maternal and neonatal sepsis, adrenal gland insufficiency and placental infarction.^{35–41} A systematic review of 19 randomised controlled trials of repeat doses of antenatal corticosteroids in animals concluded that there might be beneficial effects in terms of lung function but adverse effects on brain function and fetal growth.⁴⁰

The effect of repeat courses of antenatal corticosteroids in humans is the subject of a Cochrane review by Crowther et al.⁴² The review suggests that although repeat courses reduce the occurrence and severity of neonatal lung disease (RR 0.60, 95% CI 0.48–0.75, three trials, 2139 infants) and the risk of serious health problems in the first few weeks of life (RR 0.79, 95% CI 0.67–0.93, four trials, 2157 infants), they are associated with a reduction in some measures of weight (Z-score [weighted mean difference] –0.13, 95% CI –26 to 0.00, one trial, 1144 infants) and with being small for gestational age at birth (RR 1.63, 95% CI 1.12–2.37, two trials, 602 infants).

There is still insufficient evidence on the longer-term benefits and risks to be able to recommend the routine use of repeat courses.

The Cochrane review did not include the results of several continuing trials, two of which have been completed since its publication.^{43,44} The results of TEAMS (Trial of early and multiple steroids) are awaited.⁴³ In the MACS (Multiple Courses of Antenatal Corticosteroids for Preterm Birth) trial of 1858 women at 25–32 weeks of gestation, multiple courses of antenatal corticosteroids ($n = 937$) or placebo ($n = 921$) every 14 days until week 33 or delivery (whichever came first) found that although infants exposed to multiple courses of antenatal corticosteroids had similar morbidity and mortality to those exposed to placebo (12.9% versus 12.5%), those receiving multiple doses of corticosteroids weighed less at birth (2216 g versus 2330 g, $p = 0.0026$), were shorter (44.5 cm versus 45.4 cm, $p < 0.001$), and had a smaller head circumference (31.1 cm versus 31.7 cm, $p < 0.001$). A regime of repeat doses should not be recommended.⁴⁴

In 2000, a National Institutes of Health consensus statement concluded that 'repeat courses of corticosteroids should not be used routinely and should be reserved for women enrolled in randomised controlled trials'.⁴⁵ A recent randomised controlled trial recruited 437 patients with singleton or twin pregnancies at less than 33+0 weeks of gestation who had completed a single course of corticosteroids before 30+0 weeks of gestation and randomised them to a single rescue course of betamethasone (two 12 mg doses 24 hours apart) or placebo. There was a significant reduction in the primary outcome of composite neonatal morbidity at less than 34 weeks of gestation in the rescue steroid group than in the placebo group (43.9% versus 63.6%, OR 0.45, 95% CI 0.27–0.75, $p = 0.002$) and significantly decreased RDS, ventilator support and surfactant use.

Perinatal mortality and other morbidities were similar in each group. No long-term outcomes were reported for this study.⁴⁶

Peltoniemi et al. looked at whether a single additional dose of 12 mg betamethasone given when preterm birth is imminent before 34+0 weeks of gestation and at least a week after the full treatment course would lower the risk of RDS and severe (grade 3 or 4) intraventricular haemorrhage compared with placebo. This study showed that more infants in the steroid group required surfactant therapy. Post hoc analysis of data on 206 infants who were delivered within 1 to 24 hours indicated that the additional steroid dose tended to increase the risk of RDS and reduce the rate of intact survival. No differences were found between the steroid and placebo groups in mortality rates or rates of severe intraventricular haemorrhage. The results of this study would suggest that rescue doses may alter respiratory adaptation.⁴⁷ A subanalysis within the MACS study also showed no benefit from a rescue dose.

A rescue course of two doses of 12 mg betamethasone or four doses of 6 mg dexamethasone should only be considered with caution in those pregnancies where the first course was given at less than 26+0 weeks of gestation and another obstetric indication arises later in pregnancy.

In the absence of evidence, a rescue course of two doses of 12 mg betamethasone or four doses of 6 mg dexamethasone should only be considered with caution in those pregnancies where the first course was given at less than 26+0 weeks of gestation and another obstetric indication arises later in pregnancy. This would be justified by the paucity of data on the efficacy of the current dosing regimens on babies less than 26+0 weeks of gestation.

Source: Anceschi, M.M. et al., Effects of corticosteroids on fetal lung maturation, in: *The Surfactant System of the Lung*, MacMillan Press, London, U.K., 1991, pp. 23–27.

use of dexamethasone as the first-line treatment: four doses of 6 mg given every 12 hours. However, if dexamethasone is not available, betamethasone may be used.⁸⁵

Finally, despite the new evidence comparing single versus multiple doses of steroids, it is not possible, at this moment, to modify the recommendations of the NIH Consensus Development Panel on the use of repeated courses of ACS or to establish the number of doses or the interval between them that are safer for the fetus.⁷¹

Conclusions

If a pregnant woman has diabetes under poor control, the infant is at risk for RDS because of delayed lung maturation. The delayed lung maturation includes a delay in the appearance of surfactant and, probably, delayed lung structural maturation as a result of both high insulin and glucose effects on the fetal lung. However, concerns about the reliability of the lung maturity test in diabetic pregnancies have

decreased as management of the diabetic pregnant women has focused on the good control of blood glucose levels.

It is largely accepted that a close blood glucose control should be maintained during pregnancy, in order to reduce

complications of diabetes like macrosomia. Furthermore, when a preterm delivery is indicated such as in uncontrolled diabetic patients, it is mandatory to use a combination of tests for the prediction of fetal lung maturity.

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36 Monitoring during the later stage of pregnancy and during labor: Glycemic considerations

Harold W. de Valk and Gerard H.A. Visser

Introduction

Childbirth means a sudden change in glucose and insulin homeostasis for both the mother and the newborn child. An important threat for the neonate in the immediate postpartum period is neonatal hypoglycemia, related in part to recent maternal hyperglycemia and fetal hyperinsulinism. Irrespective of the ongoing discussion on precise cutoff levels in plasma glucose concentrations and the potential long-term consequences, current endeavors are aimed at preventing neonatal hypoglycemia as well as ensuring rapid detection and treatment. In this chapter, glycemic physiology and pathophysiology during the later stages of normal and diabetic pregnancy are briefly described followed by a description of current glucose monitoring and insulin treatment management options as well as some organizational issues.

Physiology and pathophysiology

The later stages in pregnancy are associated with an ever-increasing degree of maternal insulin resistance, brought about by placental hormones and potentially exacerbated by adipose tissue-derived interleukins, TNF- α , and other compounds. In normal conditions, the consequently increased insulin requirement is met by increasing pancreatic insulin production to maintain normal plasma glucose levels. Normal maternal plasma glucose levels imply that there are probably normal fetal glucose levels without excess stimulation of fetal insulin production. Generally speaking, insulin requirement decreases a little between 6 and 16 weeks of gestation and sharply increases after week 20. This was exemplified elegantly in a study by Mathiesen et al., using basal insulin infusion rates in women with type 1 diabetes on pump therapy.¹

In the same study, carbohydrate-to-insulin ratios (CIR) were studied. CIR signifies the number of grams carbohydrate that can be managed by 1 unit of insulin. There was a large and steady decrease in CIR during pregnancy, most notably at breakfast. This fall indicates that prandial insulin requirements (short-acting insulin) during pregnancy rise considerably, most notably at breakfast. This is a well-recognized phenomenon by patients and healthcare professionals.

In women with diabetes during pregnancy, endogenous insulin production is not sufficient to achieve normal glucose levels. In women with type 1 diabetes, this is obvious as it is in most women with type 2 diabetes. Exogenous insulin is used to imitate the normal physiological situation, but at present, we have still considerable distance to cover to reach that goal. It is wise to remind patients (and healthcare professionals as well) that part of the inability to reach glycemic targets and part of the explanation of adverse events like severe hypoglycemia are based on this inability to imitate physiology. It can do a lot to alleviate patient feeling of guilt, fear, and personal inadequacy.

In women with gestational diabetes mellitus (GDM), the ever-increasing insulin resistance, in some (obese) patients on top of an already severe degree of insulin resistance, means that maintenance of normoglycemia can only be maintained by increasing insulin production. When beta cells cannot meet this extra demand, hyperglycemia ensues. The timing of this moment depends on the degree of insulin resistance and beta-cell secretory capacity and may vary from very early in pregnancy (basically indicating a high risk of periconceptual abnormal glucose levels) to very late in the third trimester. With a fixed time for screening for GDM, these late cases are easily missed (except in the case of fetal growth acceleration but that is diagnosis of GDM and not screening for GDM) with unrecognized hyperglycemia leading to neonatal hypoglycemia in women assumed to be normoglycemic.

Glucose monitoring during later stages of pregnancy and labor

Monitoring and treatment are aimed at maintaining maternal plasma glucose levels within a safe range to prevent fetal growth promotion, to prevent maternal hypo- and hyperglycemia, and to prevent neonatal hypoglycemia. Monitoring and treatment are closely interlinked. Monitoring basically means nothing more than ensuring a steady flow of information to the patient and the healthcare professional on maternal plasma glucose levels combined with information on food intake, stress, physical activity, as well other glucose level-modifying issues and information regarding fetal growth and amniotic fluid volume. These are all essential to provide the best opportunity to improve or maintain glyce-mic control. Monitoring is a means and not a goal in itself.

The first question is at what time points do we need a measurement? Usual glycemic profiles include fasting glucose levels, preprandial glucose levels, and postprandial (1.5–2 hours) glucose levels. Fasting levels have not much to do with the culinary events during the previous evening and night. Fasting levels reflect the endogenous glucose production and is used to determine the dose of long-acting insulin or the basal rate of the insulin pump during the night. Low fasting glucose levels mean overdosing of insulin. Low preprandial glucose levels, especially if they occur at more than one meal, can indicate that the insulin dose and plasma insulin levels are too high and suppress endogenous glucose production, a key feature of the defense against hypoglycemia.

Prandial insulin doses, either by injection or by insulin pump, are determined by pre- and/or postprandial levels observed in the previous days in combination with the size and content of the envisaged meal. The dose of prandial insulin is dictated largely by the amount of carbohydrates, the content of the meal, and the degree of insulin resistance. Insulin resistance is highest during the morning and decreases during the day and is lowest in the evening and during the night, affecting insulin dosing and the CIR. It is clear that it takes clinical expertise and education from patients, diabetes nurse educators, and endocrinologists to interpret and tease out glycemic profiles especially in pregnancy and that the ability to do so is also highly dependent on the information available. This information is related not only to glucose levels but also to meals and, for example, to physical activity. More details on insulin therapy during pregnancy are described elsewhere.² Having established this framework, the second question is what the best method of glucose monitoring is.

Finger-stick measurements

Classic monitoring means glucose measurements in capillary blood obtained by finger stick. This can be painful and is cumbersome as the patient needs to carry the (small) device with her. It only provides a snapshot image of a continuously changing plasma glucose level. Kerksen et al. have shown that at least 10 measurements a day are required to

produce a profile that begins to approach informationwise that of an offline continuous glucose monitor.³ Nevertheless, part of the patient population can be well regulated during pregnancy without undue hyperglycemia or hypoglycemia. These patients basically do not need offline or online continuous glucose monitoring. In addition, some patients who could theoretically benefit from more advanced monitoring find those methods too cumbersome and too distressing, and linked to other negative emotions.

Continuous glucose monitoring

The technique of continuous glucose monitoring has been described in other chapters. Broadly speaking, two methods exist: offline continuous glucose monitoring (oCGM) and online (real time) continuous glucose monitoring (rtCGM). Both techniques measure interstitial and not plasma glucose values, but these two generally correspond well. As a consequence of measuring in two different compartments, there may be a delay in glucose curves in the compartments with the change in the interstitial compartment following the change of the plasma compartment. This delay is variable but may be as long as 20 minutes. This can pose a problem with rtCGM but not so much with oCGM.

oCGM was introduced first and provides generally up to 4–5 days of glucose values that are registered but not directly available to the patient or the healthcare professional. When we consider usefulness in the peripartum period, it is obvious that just an isolated oCGM can hardly be expected to help. The landmark trial by Murphy et al. showed that oCGM in women with type 1 or type 2 diabetes did result in a statistically significant decrease in macrosomia, the primary end point.⁴ Neonatal hypoglycemia, as an index of peripartum management, was similar in both groups (oCGM 8%, no oCGM 17%). The studied group was rather small (38 patients on oCGM and 33 patients not on oCGM), limiting the power to detect smaller differences. In conclusion, oCGM can reduce macrosomia with adequate implementation in an individualized multidisciplinary setting, but there is no specific place for oCGM in peripartum control and during delivery in patients with type 1 or type 2 diabetes. A recent Chinese study provided some evidence that oCGM may have an effect in women with GDM.⁵ In that study, patients with GDM were randomized to the intervention group (oCGM and 7-point glucose profiles) and control group (only glucose profiles). In this intensive study, the intervention group received oCGM weekly until satisfactory control was reached followed by oCGM every 2–4 weeks. They also performed glucose profiles similar to that in the control group. Nutritional counseling was based on glucose data throughout the trial. oCGM was not employed around childbirth. Insulin therapy was started significantly more in the intervention group compared to the control group (27.9% vs. 12.2%, $p < 0.001$). The incidence in the intervention group of neonatal hypoglycemia (defined as a plasma glucose < 2.2 mmol/L [40 mg/dL]) was significantly lower (5.5% vs. 14%, $p < 0.02$). Interestingly, this difference was present in

diet-treated patients but not anymore in insulin-requiring patients. In the intervention group, there was also a lower incidence of preeclampsia, primary Cesarean section, preterm delivery, macrosomia, hyperbilirubinemia, and respiratory distress syndrome. Again, these significant differences were present in diet-treated women, not in insulin-requiring women. The beneficial effect may be due to the strict nutritional setup as well as to the ability to assess the postprandial glucose curve in more detail with CGM. The lower incidence of neonatal hypoglycemia with CGM may be in part explained by the lower incidence of macrosomia. These results are reason for further studies in GDM and, if anything, underscore once the great importance of ongoing dietary counseling. At present, oGDM has no place in the peripartum management in GDM but may be a promising tool in the correct setting to reduce neonatal hypoglycemia by reducing macrosomia.

Turning to rtCGM, this technique with direct, instantaneous display of interstitial glucose levels would theoretically offer a method to optimize glucose control in a specified period of time. No studies have been performed with isolated use of rtCGM in the peripartum period. A major trial with rtCGM during pregnancy was performed by Secher et al. In that trial, pregnant patients with type 1 diabetes were randomized between intermittent use of rtCGM and no rtCGM (conventional care).⁶ No difference in neonatal hypoglycemia (defined as a plasma glucose <2.5 mmol/L [45 mg/dL]) was observed. This audacious trial has highlighted some of the issues that explain why randomized as well as observational trials are so difficult to do in this patient group. The trial showed that there was no difference in the primary outcome macrosomia. However, this lack of effect may well be explained the intermittent use (use of at least 75% of the time is mandatory to see the effects of rtCGM) as shown in the meta-analysis by Pickup et al. using the individual datasets of clinical trials.⁷ In addition, late start during pregnancy (patients require up to 6 weeks to get used to the device and practical implementation) as well as the glucose targets directing insulin therapy (prevention of hypoglycemia vs. optimal prevention of hyperglycemia) may have contributed to the negative result and indicate avenues to improve the effects of rtCGM. Trials regarding glucose monitoring are necessarily not blind (assessors may be blinded), and being in a trial usually has a beneficial effect in itself in the control group. This latest issue means that this placebo effect, which may be substantial, should be adequately accommodated in group size calculations to prevent disappointment. An earlier small study from Macedonia randomized 25 patients with type 1 diabetes on insulin pump to intermittent rtCGM or usual care.⁸ No neonatal hypoglycemia (defined as a plasma neonatal glucose of 1.66 mmol/L [30 mg/dL] or less) was observed. Neonatal hypoglycemia was not the primary end point and group size was too small to detect relevant differences when rtCGM would have had a great impact.

The Secher trial may give us some insight in the effect on neonatal hypoglycemia. Cordua et al. have looked retrospectively at the effect on neonatal hypoglycemia in this prospective trial in more detail.⁹ Neonatal hypoglycemia was

defined as a plasma glucose level <2.5 mmol/L (<45 mg/dL), the first measurement within 2 hours, and they employed prophylactic early feeding starting 3 hours after delivery in all women. In the control group, glucose was measured every hour during delivery. Such a close monitoring can mean that the difference with rtCGM may be quite limited. A sample size calculation was not performed, which is logical in a retrospective analysis. All of the women in the control group were included and 45% of the women in the rtCGM group (women had to have had rtCGM before delivery). The incidence of neonatal hypoglycemia was comparable in both groups (rtCGM 37% on rtCGM and 46% in the control group); the incidence of severe hypoglycemia (plasma glucose <2.5 mmol/L [45 mg/dL]) and intravenous glucose was similar as well (11% vs. 17%). Analysis within the group in rtCGM showed that neonatal hypoglycemia was associated with a higher mean maternal plasma glucose during the 8 hours up to delivery (either self-monitored or analyzed from rtCGM) and that the infant birth weight z-scores were inversely related to the 2-hour neonatal plasma glucose level. There was no evidence of a threshold in both associations.

This retrospective analysis of some of the data of a prospective trial highlights some important issues on research and practical management of rtCGM in the peripartum arena: the background against which rtCGM is tested (frequency of self-measurement), self-selection for rtCGM (even in randomized trials, compliance is not a random phenomenon), management of rtCGM, insulin administration technique (CSII vs. MDI), practical nutritional approach to the neonate during the first hours postpartum, definition of neonatal hypoglycemia, group size, and expected differences between groups. This illustrates that only a carefully designed large trial may give more definite answers and that, for now, common sense should prevail. Hopefully, the continuous glucose monitoring in women with type 1 diabetes in pregnancy trial (CONCEPTT) trial and the neonatal spin-off trial may shed further light on the best peripartum and neonatal policy.

RtCGM could theoretically be used during delivery as an add-on, managed by the medical team. This would obviate a large role for the delivering woman and potentially help to achieve good maternal glucose levels. On the other hand, the risk of maternal hypoglycemia may increase. No data exist on such a procedure (Figure 36.1).

Logically, preventive efforts can best be directed at those individuals at highest risk. The value of this approach has been elegantly demonstrated by Pickup who demonstrated that summarizing meta-analyses may be negative (in this case insulin pump therapy and incidence of severe hypoglycemia), whereas analyzing only those patients with prior severe hypoglycemia shows a dramatic positive effect.¹⁰

The difficulty in neonatal hypoglycemia is to define those at highest risk. Preterm delivery is a well-known one. At the end of pregnancy, we could add a large fetus (for example, with an abdominal circumference exceeding the 90th percentile) and suboptimal glycemic control with periods of definite hyperglycemia. A recent study by the Danish group may serve as a nice example, dealing with

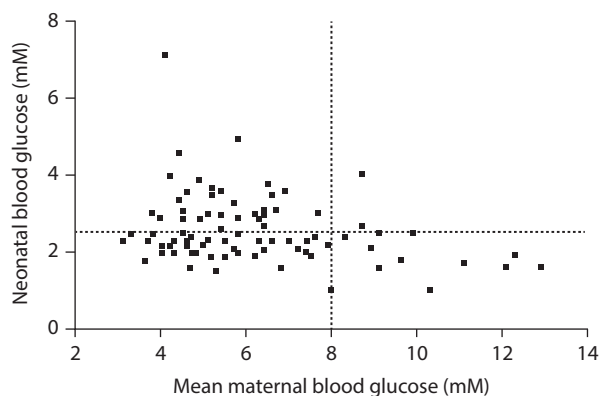


Figure 36.1 The association between maternal glucose levels and neonatal plasma glucose levels: maternal and fetal plasma glucose levels measured in capillary blood. (Reproduced from Taylor, R. et al., *Obstet. Gynecol.*, 99, 537, 2002. With permission.)

severe hypoglycemia during pregnancy.¹¹ This nonrandomized trial included women during the first trimester of pregnancy who had had at least one episode of severe hypoglycemia the previous year. Of the 28 patients, 12 (43%) chose rtCGM, and 16 chose not to (mainly for logistical reasons). The study period was the first half of pregnancy, the period of highest risk. RtCGM was used 92% of the time (in sharp contrast to the compliance in the earlier trial in pregnancy) and was associated with a dramatic and statistically significant decrease in severe hypoglycemia. This study illustrates three important issues. First, it illustrates the high compliance of patients when they have a tangible goal. Second, it illustrates the importance of selecting patients at highest risk to demonstrate a positive effect on that specific end point. Otherwise, patients at risk are drowned in a population at much lower risk, potentially diluting the positive effect into nonsignificance. Third, it illustrates the power of observational studies in glucose monitoring. This line of thinking opens new avenues of carefully controlled prospective observational real-life studies as an added research method in the scientific toolbox. Nationwide registries with good study design and adequate governance of the dataset and of the analysis may become powerful tools. The recently founded Dutch rtCGM registry (TRACING), including pregnant and preconceptional women with type 1 or type 2 diabetes on rtCGM, may provide real-life data on rtCGM use, results, and adverse events. Returning to the issue of neonatal hypoglycemia, one might consider intervention in those women and neonates at highest risk, i.e., preterm birth, large fetus, and/or suboptimal glycemic control.

Bolus calculator

In the nonpregnant state, studies have indicated that the amount of prandial insulin can be calculated by an algorithm taking into account the envisaged amount of carbohydrate

intake, the actual plasma glucose level, CIR, insulin action time, insulin sensitivity factor, and the target plasma glucose level. Use of this bolus calculator has been shown to be able to achieve an improvement in glycemic control in patients with type 1 diabetes.^{12,13} Logically, the bolus calculator could be useful in pregnancy, but data on usefulness do not exist yet. Theoretically, the ever-changing circumstances during pregnancy, in contrast to the nonpregnant state, will mean that the calculator has to be adapted very frequently. This was shown in the aforementioned study by Mathiesen et al. where prandial CIRs during pregnancy in pump-using type 1 diabetes patients fell considerably, most dramatically at breakfast. These data are in line with another study and with common experiences in the change in insulin requirements during pregnancy.¹⁴ They underscore once more the importance of ongoing dietary counseling throughout pregnancy as well as that of the care for women with diabetes during pregnancy by a multidisciplinary team. No information on the bolus calculator exists in the later stage of pregnancy and childbirth, but isolated use in that period does not seem to be a very good and practical idea. If the bolus calculator is used, this should begin much earlier, preferably before conception.

Glycemic target levels at the end of pregnancy

Part of the delivery plan is the definition of an acceptable range of plasma glucose levels. An early study by Taylor showed an inverse association between maternal glucose levels in the time leading up to the actual delivery and the neonatal plasma glucose level.¹⁵ Neonatal hypoglycemia was relatively high in case maternal glucose values were above 7–8 mmol/L (126–144 mg/dL). Using oCGM, Stenninger et al. have reported that higher maternal glucose levels are associated with a higher risk for the need of intravenous glucose in the neonate.¹⁶ The protocol in that study was already rather strict: target maternal glucose levels maximally 7 mmol/L (126 mg/dL) with subcutaneous insulin for correction of higher levels. The incidence of neonatal hypoglycemia (plasma glucose <2.2 mmol/L [40 mg/dL]) was 10 of the 15 analyzable subjects (60%) with an incidence of 5 subjects (33%) of severe hypoglycemia (neonatal glucose <2.2 mmol/L [40 mg/dL] and IV glucose). This led to the suggestion that perhaps we should aim at even lower maternal glucose levels. The retrospective analysis of peripartum glycemic control in a prospective rtCGM study also showed such an association.⁹ There are some data that the incidence of neonatal hypoglycemia may be less when targeting maternal glucose to <5.6 mmol/L (100 mg/dL).¹⁷ The consensus however is generally that a range in maternal glucose levels between 4 and 7 mmol/L (72 and 126 mg/dL) is acceptable. The absence of a threshold value leaves room for maneuvering. Common sense would dictate that one can consider a slightly higher lower level (4.5 or 5 mmol/L, 81 or 90 mg/dL) in women prone to hypoglycemia.

Peripartum insulin management

There is no definite answer to the question of what the best insulin treatment strategy is in preconceptional diabetes. Employed methods include repetitive doses of subcutaneous rapid-acting insulin above the maternal plasma glucose, continuous intravenous insulin started above a preset maternal plasma glucose level, and standard infusion of glucose combined with varying intravenous insulin infusion speed to achieve and maintain target maternal plasma glucose levels.^{16,18,19} The study by Lepercq et al. had a low frequency of neonatal hypoglycemia (13%). This low frequency may have been due to the strict maternal glucose control achieved with a combination of 10% dextrose and standard intravenous insulin to all women (although preset target levels were in the usual range, 3.4–7.8 mmol/L [61–140 mg/dL]), to a more strict definition of neonatal hypoglycemia but also to a rather aggressive approach to early neonatal management. Neonates received intramuscular glucagon at birth as well as oral suspension enriched with glucose and triglycerides during the first 3 hours after birth. Although apparently effective, it is questionable whether this scheme will find a great welcome in pediatric circles. This study demonstrates that various avenues can be taken to manage peripartum glucose and demonstrates that studies cannot easily be compared because of differences in maternal glucose target levels, definition of hypoglycemia, and postnatal management.

Organizational issues

A well-organized structure of care and counseling is of prime importance when caring for these women (and their partners and families). Good and well-based information is a first requisite, and generally speaking, information on the latter stages of pregnancy, childbirth, and thereafter is best already discussed to some extent in the earlier stages of pregnancy.

Many women find it difficult to combine a professional career with having type 1 diabetes and being pregnant. Many of them have decreased working time or stop working before formal pregnancy leave starts. In the Netherlands, for example, pregnancy leaves formally starts at 34 weeks of gestation, but many women already start descending into leave from 26 weeks onward. It is therefore wise to discuss this with the employer to prevent unpleasant surprises for all concerned. Likewise, maternity leave for women with diabetes may be too short for some women with type 1 diabetes, and this should be anticipated as well.

On a more technical level, a multidisciplinary delivery plan should be made at the most opportune moment sometime after 30 weeks of gestation. A general plan can be made for the different modes of delivery that can be individualized per patient. It is useful and advisable to provide the pregnant woman and the partner with a copy of the plan. The reevaluation of comedication after delivery and

with breastfeeding should be discussed as well as the possibility of comorbidity or change in comorbidities (diabetic complications like retinopathy but also thyroid disease or for example, preexistent rheumatoid arthritis).

Monitoring of maternal glucose levels should also be discussed including target levels and monitoring frequency. Frequent measurement of maternal glucose levels should be discussed. The frequency depends on the stage of delivery and previous glucose levels. Some women (and partners) want to manage the glucose levels, but once the actual delivery has set in, experience has taught us that all of them gladly leave it to the nursing staff. Different schemes can be used, but once every 1–2 hours is advisable (except at the beginning of an induction of labor when a more liberal time scheme can be used). Such timing issues do not exist with rtCGM, but it is advisable to register glucose levels at specified regular time points.

Neonatal management during the first days after birth is described in another chapter. Regarding the mother, there is no real need for strict glycemic control. On the contrary, as breastfeeding is associated with an increased risk of maternal hypoglycemia, a more liberal approach to target glucose levels is advisable. And with recurrent maternal hypoglycemia, hypoglycemia unawareness may ensue and complicate the situation. A practical approach would be to advise plasma glucose levels between 6 and 12 mmol/L (108 and 216 mg/dL) for a period of about 3 months.

Summary

In this chapter, we have described some issues regarding physiology and pathophysiology in the diabetic pregnancy relevant to the period of childbirth. Maternal plasma glucose levels in the period leading up to delivery and the levels during delivery are inversely related to the degree of neonatal hypoglycemia. Notwithstanding all potential benefits of advanced technology, adequate and ongoing nutritional counseling of the pregnant woman is of paramount importance. Repetitive use of rtCGM is associated with a decreased incidence of macrosomia but has no effect on the incidence of neonatal hypoglycemia in women with type 1 or type 2 diabetes. There is evidence emerging that a positive effect may be seen in diet-treated gestational diabetes. The value and possibilities offline CGM are still under debate. Audacious as these trials may be, there are many methodological issues to surmount. We hope that the current large-scale CONCEPTT trial (randomized trial with rtCGM started preconceptionally or early during pregnancy) will provide us with some answers. There is no single best insulin regimen during delivery, the choice having to be made locally. Safe target levels for maternal glucose levels are between 4 and 7 mmol/L (72–126 mg/dL) with maternal glucose levels being inversely related to neonatal glucose levels without a threshold level. The incidence of neonatal hypoglycemia depends not only on the definition of hypoglycemia but also on the specific protocol for neonatal care directly after birth.

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37 Timing and mode of delivery

Salvatore Alberico and Gianpaolo Maso

Gestational diabetes is defined by the World Health Organization (WHO) as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy.¹ The implementation of systematic screening as suggested by the evidence that emerged from the HAPO study² and the conclusion by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), who sponsored the International Workshop Conference on Gestational Diabetes in 2008, indicate that this is a frequent disease.³

In effect, the simulation assumed a gestational diabetes mellitus (GDM) prevalence of 10% according to the WHO criteria and a 50% higher prevalence (i.e., a 15% prevalence of GDM) for the IADPSG criteria.⁴

Before we go into the description of the obstetric outcome relating to pregnancies complicated by GDM, we must remember that the data available from the literature quite often do not distinguish outcomes resulting from pregnancies complicated by GDM from those with pre-gestational diabetes type 1 or 2.

According to the Pedersen hypothesis,⁵ maternal hyperglycemia results in excess transfer of glucose to the fetus resulting in fetal hyperinsulinemia. The effects of fetal hyperinsulinemia include an overgrowth of insulin-sensitive tissues such as adipose tissues, especially around the chest, shoulders, and abdomen, which increases the risk of macrosomic newborns and of shoulder dystocia, brachial plexus injury, perinatal death, and birth trauma, as well as the need for cesarean section.^{6–8}

Therefore, the prevention of excessive fetal growth during gestation, together with the proper management of maternal glucose metabolism in the anticipation of the time of childbirth, if possible, to lower the risk of foetal macrosomia, can be considered as targets to be pursued by obstetricians.¹⁰

Rate of macrosomia in diabetic pregnancy

Fetal macrosomia is varyingly defined as either an absolute birth weight greater than 4000 g, 4500 g, or 5000 g or a customized birth weight centile greater than the 90th, 95th, or 97th percentile for the infant's gestational age.

In our assessment, *macrosomia* will be considered in an infant with a birth weight greater than 4000 g. This choice is

motivated by the evidence that diabetic mothers with infants having a weight exceeding this limit exhibit a significant increase in dystocia upon birth.

GDM and even pregestational diabetes result in higher frequency of macrosomic newborns.

Four studies also allowed assessment of the association between untreated GDM according to the WHO criteria and macrosomia.^{11–14}

The pooled relative risk (RR) was 1.81 (95% CI 1.47–2.22; $p < 0.001$), with very homogenous results across studies ($I^2 = 0\%$). No study was available to examine this association using the IADPSG diagnostic criteria, but analysis using the evidence-based data group database showed an RR of 1.38 (95% CI 1.14–1.68; $p = 0.001$). When using large for gestational age as the outcome, the magnitude of the association for the WHO criteria was slightly lower (RR = 1.53, 95% CI 1.39–1.69; $p < 0.001$; $I^2 = 0\%$). Applying the criteria of IADPSG, derived from the three studies,^{15–17} we obtained a higher RR, but with heterogeneous results (RR = 1.73, 95% CI 1.28–2.35; $p < 0.001$, $I^2 = 93\%$).

Anthropometric characteristics of diabetic mothers with macrosomic infants

Studies of macrosomic infants of diabetic mothers revealed a greater amount of total body fat, thicker upper-extremity skin fold measurements, and smaller ratios of head to abdominal circumference than macrosomic infants of non-diabetic mothers. This disproportion between abdominal and cephalic diameter favors complications of childbirth, which are obviously accentuated by the greater weight of these newborns.¹⁸

The reasons are related to the fact that a normal or a proportionally lower cephalic circumference than the fetal body allows a smooth progression of the fetus in the birth canal, with normal disengagement of the head. The largest biacromial diameter involves difficulty in making an internal rotation, with the arrest of the anterior shoulder against the inner face of the pubic bone, not allowing its fixation under the margin of the same bone, and then difficulty in making a normal disengagement.

The maneuvers required to reach a fetal extraction can then lead to an excessive traction on the nerves of the brachial plexus leading to the paralysis of the same plexus.

Macrosomia: Risk factors

Macrosomia, even in the absence of a disease in a diabetic mother, involves in each case a generic risk in the obstetrical outcome.

A study investigating the effects of birth weight on fetal mortality shows that higher fetal mortality rates are associated with a birth weight greater than 4250 g in nondiabetic mothers and a birth weight greater than 4000 g in diabetic mothers.¹⁹

An interesting piece of information on the outcome of macrosomic newborns is derived from the Medical Birth Registry of Norway on 372,128 births, registered for the period 1999–2005. Especially in newborns weighing more than 4000 g, the frequency of deliveries carried out by cesarean section, particularly in emergency cesarean section, increases.

According to the same registry, fetal macrosomia leads to an increase in operative deliveries with a vacuum extractor (OR = 1.7) or low forceps (OR = 1.4) and a risk of shoulder dystocia (OR = 6.8), clavicular fracture (OR = 3.4), and plexus injury (OR = 5.6).²⁰

Fetal growth per week of pregnancy

One of the conditions that complicates child birth is certainly macrosomia, which progresses over the course of gestation. Anticipating the birth in a few weeks, after reaching the age defined as the end of gestation (≥ 37 weeks), one can therefore avoid the weekly weight gain, which in fetuses of diabetic mothers is obviously superior to a fetus with a normal progression of growth. And in fact, it is estimated that from the 37th to the 42nd week of pregnancy, weight gain may be around $625 \text{ g} \pm 201$ ($37.73 \pm 0.443 \text{ lb}$).

In the case of acceleration of fetal growth, comparable to a line coinciding with the 90th percentile, fetal weight exceeds 4000 g at the end of the 39th week of gestation.

It is so easy to imagine that in anticipation of the birth at 38 weeks, with a safe fetal maturity, it can be easier to give birth to a fetus weighing less than 500 g than compared to those who weigh more.

Shoulder dystocia: Correlation with fetal growth, GDM, and limit for vaginal delivery

Shoulder dystocia is one of the major complications that can occur during childbirth assistance of a diabetic mother's newborn. Shoulder dystocia is defined as a vaginal cephalic delivery that requires additional obstetric maneuvers to deliver the fetus after the head has been delivered and gentle traction has failed.^{21,22}

There is a wide variation in the reported incidence, and studies involving the largest number of vaginal deliveries indicate a prevalence between 0.19% and 3.3%.^{23,24}

The occurrence of shoulder dystocia involves risks not only for the newborn, which can have a permanent damage of the brachial plexus²⁵ or a greater incidence of neurological disorders, resulting in permanent neurological dysfunction,²⁶ but also for the mother. Maternal morbidity as a result of infection is increased, particularly the incidence of postpartum hemorrhage (11%) as well as third- and fourth-degree perineal tears (3.8%).²⁷

We can therefore say that shoulder dystocia is the most dangerous complication that the obstetrician is called to prevent, and the question that we must ask ourselves now is what the risk factors of shoulder dystocia are.

As we have said previously, there is a relationship between fetal size and shoulder dystocia,²⁸ but it is not a good predictor, because the large majority of infants with a birth weight of $\geq 4500 \text{ g}$ do not develop shoulder dystocia²⁹ and equally important because 48% of births complicated by shoulder dystocia occur in infants who weigh less than 4000 g.⁷

In a population of 2,014,956 deliveries, Overland et al. showed the correlation between neonatal weights and incidence of shoulder dystocia: The adjusted OR (AdOR) for a weight of less than 3500 g is 1, AdOR = 3.92 for weight between 3501 and 3999, AdOR = 17.10 for weight between 4499 and 4000 g, AdOR = 60.33 for weight between 4500 and 4999, and AdOR = 176.52 for weight greater than 5000 g.²⁹ In the same study, the condition of maternal diabetes resulted in a crude OR = 5.69 for a shoulder dystocia at delivery. Numerous other studies available in the literature have shown that the risk for shoulder dystocia has increased still to 3.6- to 4.5-fold in infants of diabetic women when the actual birth weight is $\geq 4000 \text{ g}$.^{28–33}

The debate on this issue is so open, and there are many tips that relate to the accomplishment of the delivery in pregnant women with GDM and suspected fetal macrosomia. Some authors recommend elective cesarean at an estimated fetal weight of 4000 g in diabetic patients;^{34,35} others suggest that a weight threshold of 4500 g should be used to reduce unnecessary intervention because of ultrasonographic error.³⁶

The use of the general population estimation of fetal weight as an indicator to perform an elective cesarean section is not cost-effective. The limits of predictivity of the weight using the ultrasound method are still significant for macrosomic fetuses.

It has been calculated that by placing a threshold for fetal weight $>4500 \text{ g}$, obstetricians would have to perform elective 3700 cesarean sections to prevent one permanent brachial plexus injury.

Thus, elective cesarean section for suspected macrosomia alone is difficult to support.³⁷

Different discourse appears to diabetic mothers, where if the recommendation was an elective cesarean section for estimated fetal weight greater than 4500 g, it would take 443 cesarean sections to prevent 1 brachial plexus injury.³⁸

Langer et al. instead suggested in women with GDM for elective cesarean section an estimated weight limit greater

than ≥ 4250 g during delivery. In this way, a 76% reduction of shoulder dystocia was verified in their population, with an increase in the rate of cesarean sections by only 0.26%. A weight threshold of 4500 g yielded a smaller increase in the cesarean section rate but failed to prevent approximately 40% of shoulder dystocia cases in diabetic patients.³¹

In any case, we can conclude that the class of birth weight greater than 4000 g, gestational age greater than 38 weeks, and maternal diabetes correlate directly with an increased risk of shoulder dystocia at birth.

This is the reason why many groups of experts in the management of childbirth in diabetic pregnancies establish a weight limit for vaginal birth in these women when the estimated fetal weight at 38 weeks indicates a risk of exceeding 4000 g. This recommendation takes into account the limitations of ultrasound evaluation methods to identify the correct fetal weight at term gestation. Therefore, the same recommendation is less than the limit set in the ACOG bulletin in 2005 (which established a limit of no more than 4500 g birth weight) and NICE, 2008, who indicated that limit to 4250 g.

With regard, however, to the two societies mentioned earlier, refer to the birth weight and not the fetal weight estimation assessed at 38 weeks.^{39,40}

Dystocia: Correlation with operative vaginal delivery and GDM

The same study by Øverland et al., cited earlier, clearly indicates that an additional risk factor for shoulder dystocia is represented by an operative vaginal delivery (forceps, AdOR = 1.14, and vacuum extractor, AdOR = 2.86). This risk is even more pronounced in the case of macrosomic fetuses from diabetic mothers.^{32–41}

In conclusion, we therefore could say that in pregnant women with GDM, it is prudent to avoid a prolongation of gestation, an excessive fetal weight at birth, and an operative vaginal birth in order to reduce the risk of shoulder dystocia.

Labor and delivery in GDM

The published studies on the mode of delivery in GDM indicate a common denominator: an increase in the frequency of cesarean sections. In the same studies, this rate is very high, ranging in some series from 45% to 80%.^{42,43}

A prospective case-control study (n = 3778) from Canada examined the relationship between cesarean section rates and gestational glucose intolerance (3-hour 100 g oral glucose challenge test).⁴⁴

The study identified four groups: negative gestational diabetes (n = 2940), false-positive gestational diabetes (n = 580), untreated borderline gestational diabetes (n = 115), and known treated gestational diabetes (n = 143). Women with gestational diabetes had higher rates of macrosomia (28.7% vs. 13.7%, $p < 0.001$) and cesarean section (29.6% vs. 20.2%, $p = 0.02$).

Multivariate analysis found that being treated for gestational diabetes was the most significant factor in determining a cesarean section (OR 2.1, 95% CI 1.3–3.6); untreated gestational diabetes was not a significant risk factor (OR 1.6, 95% CI 0.9–2.7) (EL = 2+).

It makes you wonder why the cesarean section rate is so high in these pregnant women. Part of the justification is related to psychological conditioning that the obstetrician undergoes in the management of these pregnancies, when the fear of having to compare with the assistance of a macrosomic child at birth associates with the forced implementation of difficult fetal extraction maneuvers in case of shoulder dystocia. We cannot ignore also the fear of having to then undergo medicolegal disputes in the event of neonatal or maternal adverse outcomes. Another hypothesis is that many of these cesarean sections are due to failed induction or labor arrest following prolonged attempts at induction.⁴⁵

A systematic review on this topic was published by Witkop in 2009.⁴⁶

This study has selected 11,400 published papers on the aforementioned subject. After a review of their structure, only five articles met the inclusion criteria for the key questions related to delivery management, and of these, only one was a randomized controlled trial (RCT) that compared the effect of two labor-induction protocols on maternal and perinatal outcomes on a population of 200 pregnancies.

Witkop says the following in his work:

The five studies were heterogeneous in their methodology, comparison groups, time period in which the study was conducted, length of the study period, populations included, and outcome measures. Because of the heterogeneity, we were unable to conduct a meta-analysis

and concludes

it is difficult to fully assess the outcomes observed in this study on the basis of only one clinical trial of 200 participants.

The study in question is that of Kjos, an RCT (n = 200) from the United States involving women with insulin-requiring diabetes comparing the outcomes of active induced labor (accurate measurement of gestational development and induction of labor with intravenous oxytocin, n = 100) with expectant management (close monitoring and insulin treatment, n = 100). Those enrolled had gestational diabetes (n = 187) or preexisting diabetes (n = 13). There were no differences between the groups at baseline. In the active induction group, 70 women had induction of labor, 8 had cesarean section, and 22 had spontaneous labor. In the expectant management group, 49 women had induction, 7 had cesarean section, and 44 had spontaneous labor.⁴⁷ This study has been shown that even after adjustment for gestational age at delivery, maternal weight, and maternal age, the average neonatal birth weight in the expectant management group was significantly greater than the mean neonatal birth

weight in the active induction group ($p < 0.01$). The findings of this RCT suggest that neonates born to women undergoing induction at 38 weeks have a significantly lower risk of macrosomia than those born to women treated with expectant management. The absence of any difference in cesarean delivery rates suggests that maternal morbidity among women undergoing induction is similar to that of women undergoing expectant management.

In a review of randomized trials of elective delivery in women with diabetes from the Cochrane database, including those with mild gestational diabetes, there was little evidence to support elective labor induction.^{48,49}

This last author forms part of the problems of management (induction vs. expectant), an important clinical factor that might suggest whether or not the opportunity to induce labor in women with GDM: the degree of ripening of the uterine cervix. In fact, he says: "Objectively evaluating the risks and benefits of labor induction is potentially confounded by the status of the cervix at the time of initiation of induction, early determination of an arrest disorder and physician bias toward cesarean delivery for women who have diabetes."

The analysis of the studies mentioned seems to agree on the benefit that induction of labor at 38 weeks in case of GDM involves a lower average neonatal weight in the induced compared to those with expectant management and a lower frequency of macrosomic newborns. In this debate, it is a rather recurrent fear that induction of labor, on the other hand, may lead to an increase in the frequency of cesarean sections.³⁵

In reference to this awe, Blackwell's study seems to contradict that induction of labor is to determine this effect. In fact, in their experience after controlling confounding factors, labor induction was not associated with the delivery mode. In fact, 55.6% of gestational and 72.9% of pregestational diabetics who achieved vaginal delivery underwent induction of labor. We agree with the conclusions of these authors, which argue that nonmedical factors may play an important role in the decision for cesarean delivery in diabetic pregnancies because they observed in their population the lack of effect of factors traditionally associated with cesarean delivery: labor induction, bishop score, epidural anesthesia, birth weight, and macrosomia.⁴²

Another support for this opinion came from the study of Levy, who, in a retrospective cohort study using routinely collected data ($n = 108,487$) undertaken in the United States, examined whether induction of labor increased cesarean section rates in women with diabetes. The cesarean section rate was lower in women who had induction of labor than those who did not have induction of labor (OR 0.77, 95% CI 0.50–0.89) (EL = 2+).⁵⁰

International societies: What recommendations do they suggest?

Very briefly, we indicate the recommendations that the most important societies of obstetrics and gynecology suggest in reference to the weight limit for carrying an elective cesarean

section in diabetic pregnancies and the opportunity to lead or not an induction of labor.

American Society of Obstetricians and Gynecologists

1. A cesarean delivery may be considered if the estimated fetal weight is greater than 4500 g in women with diabetes.
2. Expectant management beyond the estimated date generally is not recommended. Induction of labor in pregnancies with a fetus with suspected macrosomia has not been found to reduce birth trauma and may increase the cesarean delivery rate.³⁹

Colorado clinical guidelines

- Timing of delivery remains relatively open. There are no data to support delivery prior to term or cesarean delivery purely on the basis of GDM.
- Well-controlled GDM pregnancies on medical nutrition therapy have little indication for delivery prior to 38–39 weeks gestation.
- Delivery at ~39 weeks gestation has been shown to decrease macrosomia in women with good dating criteria and a favorable cervix.
- To determine the mode of delivery when the estimated fetal weight is 4000–4500 g, consider past delivery history and clinical pelvimetry.⁵¹

Collège National des Gynécologues et Obstétriciens Français

1. Elective cesarean section in the case in which the estimated ultrasound fetal weight indicates a value greater than >4250 to 4500 g.
2. It is possible to propose an induction of labor at term (>39 weeks) taking into account a balance of benefit to the mother and the fetus.⁵²

Austrian guidelines

1. Timing of delivery was not determined in the Austrian guidelines for gestational diabetes management.
2. Continue pregnancy until term when uncomplicated; aim for vaginal delivery if possible.⁵³

Australian guidelines

1. Induction of labor or operative delivery based on obstetric and/or fetal indications; otherwise deliver at term.⁵⁴

Royal College of Obstetricians and Gynecologists

1. Induction of labor at term can reduce the incidence of shoulder dystocia in women with gestational diabetes (Grade B).
2. A systematic review and meta-analysis of RCTs of the effect of treatment in women with gestational diabetes³⁸ concluded that the incidence of shoulder dystocia is reduced with early induction of labor.

3. The NICE diabetes guideline recommends that pregnant women with diabetes who have a normally grown fetus should be offered elective birth through induction of labor, or by elective cesarean section if indicated, after 38 completed weeks.
 - a. The NICE induction of labor guideline recommended that women with pregnancies complicated by diabetes should be offered induction of labor before their estimated date of delivery.⁴⁰
4. Elective cesarean section should be considered to reduce the potential morbidity for pregnancies complicated by preexisting or gestational diabetes, regardless of treatment, with an estimated fetal weight greater than 4500 g.⁵⁵

Italian guidelines

1. Pregestational and gestational diabetes are not in itself an indication for cesarean section.
2. In the case of estimated fetal weight ≥ 4500 g, cesarean section from 38 + 0 weeks gestation is recommended.
3. Pregestational and gestational diabetes are not contraindications to vaginal birth after previous cesarean section (VBAC).⁵⁶

Timing

The timing of induction in the case of GDM must meet two requirements: (1) must be performed at a time that the fetus reaches lung maturity (delayed in diabetic pregnancy), and (2) before fetal growth reaches a point that increases the risk of shoulder dystocia.

Most of the studies have identified issues related to GDM in the 38th week of gestation. Moreover, this limit is the one proposed by NICE, no. 63/2008, which reads as follows: "Pregnant women with diabetes who have a normally grown fetus should be offered elective birth through induction of labor, or by elective cesarean section if indicated, after 38 completed weeks."^{40,47–57}

Induction or expectant management

Evidence in the literature about the best management possible (induction vs. expectant) in women with GDM are therefore neither strong nor unique. For this reason, we decided to design a multicenter RCT on this topic, GINEXMAL (Gestational Diabetes Mellitus: Induction vs. Expectant Management Labor), in order to understand whether the induction of labor at 38 weeks actually produces an increase in the rate of cesarean sections in front of the undisputed benefit of reducing the frequency of macrosomic births.

In a previous study, it had in fact occurred retrospectively that labor induction at 38 weeks in GDM patients with fetal growth acceleration does not seem to determine an increased

Table 37.1 Patients in study

	Induction	Expectant	<i>p</i>
Number of recruited pregnancies: 371	186	185	
Neonatal average weights	3200 g	3420	$p < 0.001$
Cesarean section (11.8%)	12.9%	11.4%	n.s., $p = 0.6$
CS + operative vaginal delivery	19.4%	21.6%	n.s., $p = 0.6$

incidence of C-section in comparison to expectant management, particularly in case of maternal obesity.⁵⁸

The GINEXMAL RCT is expected to enroll women with GDM at 38 weeks, with singleton pregnancies in cephalic presentation with no previous cesarean section, excluding pregnant women with an estimated weight of more than 4000 g at 38 weeks. The assignment is in two arms: induction at 38 weeks vs. expectant management until 41 weeks, where induction of labor is carried out.⁵⁹

It was not easy to complete this trial, because as stated, verbatim, by Witkop in his work: "We acknowledge the potential barriers to the conduction of clinical trials in pregnant women. Clinical trials of labor management may be particularly difficult in the current highly litigious environment. The feasibility of trials might also be influenced by patient preferences for care and provider perception of patient risks."⁴⁶

The recruitment of patients was completed in April 2014. The interim data measured at November 2013 are presented in Table 37.1.

Therefore, the conclusions that can be drawn on these preliminary assessments are as follows:

- The averages of the weights of newborns in the induction group are significantly lower than those of the expectant group.
- Induction does not increase cesarean section.
- Reduction of cesarean section + operative vaginal delivery in induction (n.s.).
- Low rate of cesarean section in all the recruited population (11.8%).

Special clinical conditions

Obesity

An obese patient (body mass index > 30) with GDM has specific risk factors in labor that most often lead to an emergency cesarean section.⁶⁰

It is also known that obesity is associated with an increased risk of failed labor induction that appears to be related directly to an increasing class of obesity.⁶¹

This is confirmed by several observational studies available in the literature but has also been shown by some studies carried out by S. Quenby on the characteristics of the muscle cells of the uterus. She noted that in obese subjects, a higher concentration of cholesterol is present at the level of these fibrocells, which induces a dysfunction in labor, of uterine contractions, which then lose their effectiveness.⁶²

Vaginal birth after previous cesarean section

Vaginal delivery and the induction of labor are not contraindicated even in cases of GDM; a retrospective case series ($n = 10,110$) from the United States examined the success of VBAC in women with previous obstetric complications, including gestational diabetes.⁶³ Sixty-two percent of women who attempted VBAC were successful. The factors associated with unsuccessful VBAC were birth weight exceeding 4000 g, cephalopelvic disproportion, prolonged labor, dysfunctional labor, preexisting diabetes and gestational diabetes, hypertension, induced labor, sexually transmitted disease, fetal distress, and breech birth.

Another retrospective cohort study ($n = 25,079$) from the United States showed instead that gestational diabetes is not an independent risk factor for VBAC.⁶⁴ The study involved 13,396 women who attempted VBAC. Data on 423 women with diet-controlled gestational diabetes and 9437 women without diabetes were analyzed. The success rate for attempted VBAC among women with gestational diabetes was 70% compared to 74% for women without diabetes, and the proportion of babies weighing more than 4000 g was 18% compared with 13% ($p < 0.05$).

Glycemic profile during labor and risk of fetal death in GDM

We do not feel superfluous to recall once again the importance of maternal glycemic control during labor and birth and early feeding of the baby in order to reduce the risk

of fetal distress and neonatal hypoglycemia (*NICE Clinical Guideline no. 63*).

Conclusion

The recommendations concerning guidelines must be based on randomized, controlled clinical trials. The two RCTs available in this area (GL Kjos and GINEXMAL) indicate with certainty that in women with GDM, the induction of labor produces an average of neonatal weights lower than in the group with expectant management with a lower frequency of macrosomic births.

Lowering the frequency of macrosomic births in women with GDM without increasing the rate of cesarean sections can already be considered an important positive result.

The selection of patients eligible for an active management, which takes into account the degree of cervical ripeness, can help lower the frequency of cesarean sections in the induction group.

The recommendations that we can try to define with regard to the opportunity to induce labor in childbirth are therefore as follows:

- The induction of labor at 38 weeks is justified in order to reduce the frequency of births with higher weight. The effect leads to known benefits associated with the birth of a reduced number of macrosomia.
- It is good to act with *common sense* according to the clinical characteristics of the patient, her Bishop's score, and her motivations.
- It is also important to have one part of a comprehensive informed consent from the patient and the other of a full capacity to manage the complications of delivery by consultants.

Finally, it should be remembered that a clinical recommendation is, however, a suggestion aimed at intelligent professionals where they can customize the interests of patient care, and not a military order to be executed at all costs.

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38 Management of the macrosomic fetus

Federico Mecacci, Marianna Pina Rambaldi, and Giorgio Mello

Introduction

Despite major progress made in obstetrics over recent decades, there is still a lack of knowledge on how to manage the macrosomic fetus. Attention has always been mostly focused on the opposite extreme of the scale of growth, thus resulting in a gap in the literature on the management of large fetuses. Published studies do not even find a consensus on the definition and are designed primarily to detect complications during labor, those that question the outcome of the pregnancy are dated, and there is no meta-analysis.

Definition and diagnosis

Macrosomia is diagnosed in the presence of excessive intra-uterine growth resulting in a birth weight that exceeds an established limit of either 4000 or 4500 g.¹ Approximately 10% of all newborns have a birth weight of >4000 g, 1.5% weigh >4500 g, and 0.1% weigh >5000 g.^{2,3} The American College of Obstetricians and Gynecologists recommends the use of the 4500 g threshold because morbidity increases sharply beyond this weight, but acknowledges that there is some increased risk of complications at weights >4000 g.¹ This definition does not take into account the population distribution, in which large fetuses are defined as those who weigh more than the 90th percentile for gestational age. Weight percentile is the best means for identifying the preterm macrosomic fetus (Table 38.1).

Regardless of the definition used, diagnosis of macrosomia is difficult and often inaccurate. Symphysis–fundal measurements combined with Leopold maneuvers showed sensitivities of only 10%–43% and positive predictive values of 28%–53% for detecting macrosomia.⁴ Although these results appear suboptimal, the use of ultrasonography examination does not improve the detection rate.¹ When 2D ultrasound scan is used for the diagnosis of macrosomia, the estimated fetal weight (EFW) obtained with the Hadlock's formula was found to have a higher predictive value compared to other methods.^{5,6} Nevertheless, EFW formulas perform better for appropriate-for-gestational-age fetuses; i.e., the Hadlock's formula increases the absolute mean percentage of error from 8% to 13% when used for infants larger

than 4500 g.^{3,7–10} A review of 14 studies on the detection of macrosomia (≥ 4000 g) using different methods for sonographic EFW reported widely varying results: sensitivity of 12%–75%, specificity of 68%–99%, and posttest probability of 17%–79% after a positive test.³ The diagnosis of macrosomia defined as ≥ 4500 was even less accurate. The error is partially explained by the fact that ultrasound does not take into account body composition; because of this factor, it can be a substantial variation in birth weight even among fetuses with the same biometric parameters. An additional error factor is the increased incidence of diabetes in mothers of macrosomic fetuses; in fact, Hadlock's formula is very sensitive to abdominal circumference measurement that is increased in these fetuses.

Complications

Macrosomic fetuses are at increased risk of complications during pregnancy, childbirth, and postnatal life in the short and long term (Table 38.2). In this chapter, we will only review the risks related to pregnancy (for other complications, see Chapters 40 through 48).

The birth weight–specific infant mortality curve shows a decline in mortality with increasing birth weight until a point at which the slope reverses and the mortality rises again for fetuses situated at the upper values of the curve. High birth weight has been associated with a two to three times risk of intrauterine death.^{11–14} The most recent study published on this topic found that fetuses weighing 4500–5000 g had an odds ratio of 2.7 (95% CI, 2.2–3.4) to die in utero compared to fetuses of appropriate weight (3500–4500 g), while fetuses who weigh >5000 g had a 13.2 times greater risk (95% CI, 9.8–17.7). Furthermore, both categories were at higher risk of morbidity, especially birth injury and low 5-minute Apgar score.¹¹

Prevention of stillbirth in large fetuses is challenging and the most effective measure still remains the prevention of macrosomia by a more careful management of maternal risk factors during the preconceptional period or as early as possible in pregnancy. It is debated whether it would be possible to prevent stillbirth, anticipating the deliveries of all at-risk

Table 38.1 Risk factors for having a macrosomic infant

Previous macrosomic infant
Maternal prepregnancy weight
Excessive weight gain in pregnancy
Maternal diabetes
Multiparity
Male infant
Postterm pregnancy
Hispanic or African-American ethnicity
Maternal birth weight over 4000 g
Maternal height
Maternal age younger than 17
Advanced maternal age

Table 38.2 Short-term complications

Shoulder dystocia
Birth injuries
Mechanical ventilation for more than 30 min duration
A 5-minute Apgar score <3
Respiratory distress syndrome
Meconium aspiration
Perinatal mortality

pregnancies at 38 weeks; however, an analysis of the literature suggests that the majority of fetal deaths occur before this term and therefore would not be prevented with early induction.^{15–17}

Short-term maternal complications reported in association with fetal macrosomia are increased rate of cesarean section, perineal lacerations, uterine atonia, and postpartum hemorrhage.¹⁸ The risk of emergency cesarean section is reported to be nearly double and the risk of grades III and IV lacerations can be three to six times higher when the birth weight is above 4500 g.^{19,20}

Intervention

Currently, there is a lack of evidence in the literature on the possibility of and on which could be the best way to treat fetal macrosomia. For mothers without diabetes, no clinical interventions have been reported to be useful. In this population, the best recommendation could be to prevent the development of macrosomia with dietary intervention in women at risk for obesity or excessive weight gain, but no randomized controlled trials have been conducted yet. For pregnancies complicated by diabetes, it seems possible to improve fetal outcome, adding insulin to the diet when macrosomia is diagnosed between 29 and 33 weeks of gestation.²¹

Antenatal monitoring

There is no standardized algorithm for performing antenatal monitoring of fetal macrosomia.

The macrosomic fetus is in a fragile balance; its large constitution and enhanced metabolism result in an increased oxygen need with respect to an average-weight fetus, while its placenta is not equally developed to accommodate this request and may induce a chronic status of fetal hypoxemia.^{22–24}

The two main risk factors for macrosomia are obesity and gestational diabetes and, when present, may complicate the clinical management at term. On one hand, obese women are at increased risk of complication because the adipose layer limits the maternal ability to perceive fetal movements and at the same time limits the diagnostic accuracy of ultrasonography investigation. In addition, if diabetes is the cause of macrosomia, reactive fetal hyperinsulinism acts on the placenta. Insulin has a direct effect on the fetal placenta, inducing alterations in endothelial gene expression and stimulating the synthesis of glycogen at this level, determining a thickening of the membrane that worsens fetal hypoxia.

There is no data from large or randomized trials to formulate evidenced-based recommendations on which pregnancies complicated by macrosomia should undergo fetal surveillance, when to start it, what test to order, or how often to perform it. The authors suggest antepartum monitoring using fetal movement counting, biophysical profile, and non-stress test (NST) starting from 37 weeks of gestation and performed at least weekly until 40 weeks.

Induction of lung maturity

When considering an elective early delivery because of fetal macrosomia, it must be taken into account whether there is sufficient fetal maturation. As the morbidity associated with early term and late preterm deliveries in general obstetric population has become evident, elective delivery before 39 weeks is increasingly discouraged.^{25,26} Furthermore, respiratory distress syndrome is more likely to develop in infants of women with diabetes delivered early than in infants of women without diabetes; this risk does not become equivalent in the two groups until after 38.5 weeks of gestation.²⁷ It is debated whether it is appropriate to test for lung maturity if delivery is anticipated before 39 weeks, also because it has been shown that a positive result does not obviate all the complications associated with late preterm birth.²⁸

Conclusions

- Diagnosis of macrosomia is often inaccurate and ultrasonography does not perform better than clinical examination with symphysis–fundal measurements combined with Leopold’s maneuver. Pregnancy affected by macrosomia poses an increased risk for the fetus and the mother.
- No strategy has proved to be effective in reducing complications once the macrosomia is present in nondiabetic pregnancies.
- Further studies are needed to define the best way to monitor macrosomic fetuses at term.

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39 Congenital malformations in diabetic pregnancy: Prevalence and types

Paul Merlob

Introduction

The association between maternal diabetes mellitus and congenital malformations in newborns may well be causal; however, the teratogenic mechanism remains unclear.¹ The prevalence and the described type of malformations vary among different studies, and a predictable malformation syndrome has not been identified.¹ This chapter discusses the prevalence and types of structural congenital malformations in infants of mothers with diabetes mellitus (IDM) or gestational diabetes mellitus (IGDM). Their etiology and pathogenesis are presented in two other chapters of this book.

Historical data

Many studies of small groups of infants (from 1930 to 1950), including malformed infants, were not conclusive. It was only after 1960 that large, controlled, population- or hospital-based studies of offspring of mothers with diabetes began to appear in the literature.

In 1964, Molsted-Pedersen et al.² studied 853 IDM born between 1926 and 1963 and weighing more than 1000 g. They noted a 6.4% rate of congenital malformations, compared to only 2.1% in a control group of 1212 infants born to nondiabetic mothers in the same hospital, but during 1958 and 1960.

Further analysis revealed that the presence of maternal vascular complications was associated with a significantly greater risk of fatal, major (but not mild), and multiple malformations in the infants.

Two years later, Naeve¹ analyzed the frequency of congenital malformations in infants of 2592 diabetic mothers, 892 women known to have become diabetic 5 or more years after delivery, and 1262 infants of women married to diabetic men and an equal number of infants of nondiabetic pregnancies. A significantly higher rate of congenital malformations was noted in the study group (13.1%) than in

the control group (5.3%), with a relative risk of any malformation of 2.47. The frequency of malformations increased steadily with the severity of the maternal diabetes scaled by White's classification.

The largest review of malformations associated with diabetic pregnancy, performed by Kucera³ in 1971, included the data available from the world literature between 1945 and 1965, covering 7101 infants born to diabetic mothers and a control group of more than 400,000 healthy infants derived from the registries of the World Health Organization. The prevalence of congenital malformations was 4.79% in the study population compared with 0.65% in the controls.³ However, information regarding the criteria used for the diagnosis and management of diabetes, and for the diagnosis and classification of the malformations, was not consistently available.

The results of the Collaborative Perinatal Project, using data from hospitals throughout the United States, were reported in 1975.⁴ A total of 567 overt diabetic pregnancies, 372 gestational diabetic pregnancies, and 47,408 nondiabetic pregnancies were analyzed. Congenital malformations were identified in a significantly higher proportion of infants of mothers with overt diabetes (17.1%) than in infants of nondiabetic mothers (8.4%). The IGDM had an 8.9% rate of malformations, almost equal to that of the control group.

In 1976, Soler et al.⁵ studied 701 IDM born in Birmingham, United Kingdom, between 1950 and 1974, of whom 8.1% were found to have a congenital malformation compared to 1.7% in the control group. In the same year, Day and Insley,⁶ in a study of 205 IDM born in the same area between 1969 and 1974, reported a malformation rate of 12%, compared to 6% in the control nondiabetic group.

After 1980, investigations in the field expanded worldwide. Although their specific figures differed considerably, in almost all of them, the prevalence rates were significantly higher in IDM than in the general newborn population. However, even the largest studies⁷⁻¹¹ comprised a relatively small absolute number of congenital malformations in

offspring of women with pregestational insulin-dependent diabetes.¹¹ Recently (2012), the largest case series of malformed babies (669 newborns) was published by Garne et al.¹² confirming that the risk of major nonchromosomal congenital anomalies is at least twice as high in the pregestational diabetic pregnancies compared to nondiabetic pregnancies.

Prevalence

The prevalence of congenital malformations has been evaluated predominantly in women with type 1 diabetes (pregestational insulin-dependent diabetes), with rates ranging mainly from 4.1% to 17.1%. Despite improvements in obstetric care, with strict control of diabetes and good pregnancy surveillance, the rate of major malformations in infants of mothers with type 1 diabetes remains two to three times that of the general population. Comparisons among the different studies are very difficult, if not impossible, for several reasons:

- The diagnostic classification of diabetes varies among and even within countries.
- Screening for the detection of diabetes has not been undertaken in the same manner and scale in all geographic regions.
- The timing and degree of preconception and postconception care differs.
- The diagnosis, definition, and classification of congenital malformations vary largely among studies.
- The methods used to detect fetal and neonatal malformations are different.
- Other confounding factors, such as maternal age, obesity, ethnicity, and uptake of folic acid, are rarely taken into account.

These confounding factors may explain the great variability in the reported prevalence rates of congenital malformations in type 1 diabetic pregnancies, and they should be taken into account when prevalence of malformations is studied.

It is important to emphasize that the demographic pattern of diabetes in pregnancy is changing: increasing numbers of young women are being diagnosed as having type 1 diabetes, and the number of people diagnosed as having type 2 diabetes is also increasing.^{13,14}

With regard to gestational diabetes, several authors have reported an association with major malformations, and the same types of anomalies were found as in the offspring of women with pregestational type 1 diabetes.^{8,15–18} Although the risk is apparently lower, being that gestational diabetes accounts for approximately 90% of all cases of pregnancies complicated with diabetes,¹⁹ the overall effect of this risk has important clinical and public health connotations.

Sheffield et al.¹⁰ found that women with pregestational diabetes or gestational diabetes plus fasting hyperglycemia had a threefold to fourfold greater risk of congenital malformations in their offspring than the general population, whereas infants of women with mild gestational diabetes had

malformation rates no different than the general nondiabetic population. Nevertheless, it is important to remember that gestational diabetes is a heterogeneous disorder that includes previously unrecognized or newly diagnosed nongestational diabetes mellitus.^{8,17} These patients (with preexisting but undetected type 2 diabetes) represent a subgroup of IGDM with an increased risk for occurrence of congenital malformations.

Type 2 diabetes (associated with both increasing insulin resistance and abnormality of insulin secretion) is increasing explosively.^{13,20} As in all diabetic pregnancies, infants born to mothers with type 2 diabetes are also at increased risk of having congenital malformations.^{16,20} The most common malformations²⁰ were cardiac (53%) followed by musculoskeletal (27%). These results are almost similar to rates previously identified in women with type 1 diabetes.²⁰ The majority of malformations occurred in those with poor glycemic control who did not received prepregnancy care.^{20,21}

The prevalence of congenital malformations in all types of maternal diabetes is in good relationship with

- The severity of the maternal diabetes (White's class)
- The control of maternal diabetes (expressed by HbA1c)

An increased prevalence of malformations occurring in parallel with the severity and duration of the diabetes has been described.²² For example, the frequency of major malformations among offspring has been reported to be 4.4% in White's classes B and C, 9.7% in class D, and 16.7% in class F, with an overall prevalence of 6.4% in all infants of diabetic mothers as compared with 2% in the general population.²²

The same increase of prevalence of malformations was observed in relation to the HbA1c levels. For example, a frequency of 5.1% of malformations has been reported for a HbA1c of 7.0%–8.5%, 22.9% for a level of 8.6%–9.9% and 21.7% for a level of HbA1c above 10%.²² Even a slightly raised of HbA1c during early pregnancy in women with type 1 diabetes carries an increased risk for fetal malformations.^{23,24}

Types of malformations

The congenital malformations of IDM and IGDM constitute a spectrum known as diabetic embryopathy (DE).^{12,22,25} This spectrum implies errors of morphogenesis that appear between the third and the seventh week of embryonic development (end of blastogenesis and organogenesis).²⁶ Within this spectrum of DE, cardiac, skeletal, central nervous system (CNS), urogenital, gastrointestinal, facial, and multiple malformations were repeatedly described (Table 39.1). Congenital malformations in IGDM and offspring of women with type 2 diabetes affect the same organ systems that have been previously described in pregnancies with type 1 diabetes.¹⁶

The most commonly affected organ systems were cardiac (37.6%), musculoskeletal (14.7%), CNS (9.8%), and multiple malformations (16%).¹⁶

Table 39.1 Congenital malformations in infants of diabetic mothers

Organ system	Malformations	
	Common	Rare, occasional
Cardiac	Corrected transposition	Tetralogy of Fallot
	Ventricular septal defect	Hypoplastic left heart
	Coarctation	Single ventricle
	Atrial septal defect	Double-outlet right ventricle
	Cardiomyopathy	Pulmonic stenosis
Skeletal		Anomalous venous return
	Sacral agenesis	Polydactyly
	Vertebral and rib anomalies	Syndactyly
	Limb reduction defects	Clinodactyly
CNS		Clubfoot
	Anencephaly	Occipital encephalocele
	Neural tube defects	Holoprosencephaly
	Microcephaly	Septo-optic dysplasia
Urogenital	Hydrocephalus	
	Hydronephrosis	Hypoplastic genitalia
	Renal agenesis	Micropenis
	Ureteral duplication	Ambiguous genitalia
	Multicystic dysplasia	Megalo-urethra
Gastrointestinal	Hypospadias	
	Duodenal atresia	Malrotation
	Anorectal atresia	Volvulus
	Esophageal atresia	Omphalocele
		Gastroschisis
Facial		Diaphragmatic hernia
	Cleft lip	Choanal atresia
	Cleft palate	Absent depressor anguli oris muscle
	Ears	Fused orbits
	Microtia	
	Anotia	
	Atresia of canal ear	
	Hairy ears	
	Hearing loss	
	Eyes	
	Cataract	
	Coloboma	
	Optic nerve hypoplasia	
Others	Single umbilical artery	Laterality defects
		Tracheal stenosis
		Branchial arch anomalies

It has been debated whether maternal diabetes exerts a nonspecific teratogenic effect expressed in a universally increased risk of all congenital malformations or whether the disease should be regarded as a specific teratogen associated with a distinct pattern of congenital abnormalities.¹¹ The spectrum in DE is large and highly variable; however, most studies have reported an increase of specific malformations especially involving the heart, the skeleton (particularly sacral agenesis), the kidneys, and the CNS.⁷ Regarding

cardiac malformations, the strongest association with maternal diabetes was found in infants with defects of primary congenital cardiogenesis, whereas most abnormalities arising later in cardiac development were not associated with diabetes.⁹ Others found a strong teratogenic effect on four specific types of malformations: renal agenesis, obstructive urinary tract, and cardiac and multiple abnormalities, as opposed to an unspecific increased general risk of congenital malformations.¹¹

Cardiac malformations

Cardiac malformations are the most common congenital malformations of IDM, and they occur significantly more often in IDM than in infants of nondiabetic mothers.^{7,12,22} Rowland et al.²⁷ reported a 4% prevalence of cardiac malformations in a series of 470 IDM, a fivefold higher rate than in the general population (0.8%). Becerra et al.⁷ found that IGDM who required insulin during the third trimester of pregnancy were 20.6 times more likely to have major cardiovascular malformations than infants of nondiabetic mothers. No such difference was noted in IGDM who did not require insulin.⁷

Loffredo et al.,⁹ in a population-based case-control study of 4390 IDM and 3572 healthy infants, observed that preconceptional maternal diabetes was strongly associated with cardiovascular malformations of early embryonic origin (OR = 4.7) and cardiomyopathy (OR = 15.1), but not with obstructive and shunting defects (OR = 1.4). There was a strong association of cardiovisceral and cardiac chamber discordance, i.e., “corrected” (levo-) transposition of the great arteries, but not with “pure” transposition, i.e., intact ventricular septum or ventricular septal defect.⁹ Among outflow tract anomalies, the risk was strongly associated with normally related great arteries (OR = 6.6) but not with simple transposition. These findings imply a specific effect of maternal diabetes on certain subtypes of cardiac malformations and may have important clinical and preventive implications.⁹

Skeletal malformations

Maternal diabetes has been associated with sacral agenesis, also termed sacral dysgenesis or caudal regression.³ This is a complex malformation characterized by the absence or maldevelopment of the sacrum and coccyx, with or without hypoplastic femurs, dislocated hips, defects in tibias or fibulas, or other lower-limb malformations. Affected babies often have anomalies of other organ systems as well. Sacral agenesis occurs in about 0.2%–0.5% of IDM, representing a 200- to 400-fold higher rate than in the general population.^{5,12,22} Another skeletal malformation, proximally placed preaxial hallucal polydactyly, particularly when coupled with segmentation anomalies of the spinal and tibial hemimelia, seems to be highly suggestive of DE.²⁸

CNS malformations

Anencephaly is the most common CNS malformation associated with diabetic pregnancy, affecting 0.57% of IDM,²² which is threefold higher than the rate in the general population (0.19%).²² IDM also have a high prevalence of neural tube defects (1.95% vs. 0.2% in the general population).²⁹ One study of experimental diabetes induced after the period of organogenesis noted no effect on the CNS of the offspring.²²

Urogenital malformations

Kucera³ was the first to report an increased rate of urological malformations in IDM. The most frequent renal

malformations in IDM are renal agenesis, ureteral duplication, and hydronephrosis.^{1,11,25} Hypospadias is the most frequent genital malformation in IDM and IGDM.^{11,25}

Gastrointestinal malformations

The abdominal malformations shown to occur with a higher prevalence in IDM include anorectal, duodenal, and lower intestine atresia.^{22,25} Malrotation, volvulus, and abdominal wall defects have also been described.

Facial malformations

Facial anomalies in IDM and IGDM have been described in only a small number of reports.^{7,17,30–33} The most frequent were orofacial clefts^{7,17} and ear and eye abnormalities.^{1,7,31} Interestingly, some studies reported an association of maternal diabetes with certain facioskeletal syndromes, such as femoral-facial syndrome and oculoauriculovertebral polytopic field defect.^{31–34} Therefore, IDM and IGDM should be carefully evaluated for facial malformations.^{31–34}

Other anomalies

A single umbilical artery occurs in about 6.4% of IDM, a fivefold higher rate than in the general population.²² This mild malformation might be associated with other, major, structural anomalies.

Multiple malformations

Many studies found a strong association between pregestational maternal diabetes and multiple-system malformations (not defined as a syndrome) in the offspring.^{4,11,12} For example, 27.5% of all malformed infants in the Collaborative Perinatal Project 4 had multiple anomalies. Aberg et al.¹⁷ observed that 6% of their malformed IDM had more than one anomaly compared to 0.57% of the control group. They concluded that there is a clear-cut increase in the risk of multiple malformations in infants of mothers with preexisting diabetes, but not of mothers with GDM.¹⁷ In the infants with multiple malformations, the same organ systems were affected as in the whole group of IDM, with highest rates for cardiac malformations, atresias, clefts, limb reduction, and hypospadias.

Mild malformations

Studies on mild malformations in IDM and IGDM are relatively scarce,^{35–37} and no randomized double-blind investigations have been performed to date. The results of the case-control studies are contradictory, with some showing significant differences but others not. No association was observed between the severity of the metabolic derangement (HbA1c) in the mother and the appearance of mild malformations in the offspring.^{36,37} This was also true for White's class, duration of diabetes, maternal age, and cigarette smoking.³⁵

Preconception care and reduced risk of congenital malformations

Many prospective controlled studies worldwide have demonstrated that strict metabolic control of maternal diabetes before conception and during pregnancy can prevent most neonatal complications, including congenital malformations.³⁸ Ray et al.²¹ conducted a systematic review of all published studies on preconception care (PCC) (eight prospective and eight retrospective studies were included in the final analysis) involving a total of 1192 infants whose mothers had received PCC and 1459 infants of mothers who had not. The pooled rate of major malformations was lower in the infants of the PCC recipients (2.1%) than in nonrecipients (6.5%), with a relative risk of 0.36. Interestingly, the risk of major malformations was lowest in the one study in which folic acid was administered periconceptionally.³⁹ Recently, Correa et al. in a multicenter, population-based case-control study of birth defects, found that lack of periconceptional vitamins or supplements that contain folic acid may be associated with an excess risk for birth defects due to maternal diabetes mellitus.⁴⁰ The essential problem is that a substantial percentage of diabetic women do not attend PCC programs²¹ and do not take prenatal folic acid and multivitamins, just as in the general population.⁴¹ Greater efforts by

the medical community are needed to promote education of the public, improve maternal access to PCC programs, and maximize the interventions associated with improved pregnancy outcome.²¹

Summary

Maternal diabetes mellitus (types 1 and 2) and gestational diabetes with fasting hyperglycemia are associated with a twofold to threefold increase in the risk of congenital malformations in offspring compared with the general population. Although no specific malformation syndrome has been identified, cardiac, skeletal, CNS, and multiple malformations are the most frequently described. Up to 50% of all perinatal deaths of offspring of diabetic mothers are due to congenital malformations.⁴² Congenital malformations also pose a serious social and financial burden to both the individual family and society at large.²² Therefore, the medical community must ensure that programs for PCC are made available to diabetic mothers for strict control of their disease before conception and during pregnancy. This could prevent the occurrence of most neonatal complications, including congenital malformations.

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40 Diabetic embryopathy in the preimplantation embryo

Asher Ornoy and Noa Bischitz

Introduction

Diabetes mellitus can also cause, in addition to birth defects and/or intrauterine death, decreased fertility in males and females. As maternal diabetes may affect embryonic development at different developmental stages, an important question relates to the stage at which the developing embryo may be affected. Does the first fault occur at the zygote, morula, blastula, or perhaps even earlier, at the oocyte phase?

This chapter will discuss the influence of maternal diabetes on the embryo at the preimplantation and preorganogenetic phase, i.e., the first week postfertilization in rodents and the first 2 weeks in man.

The preimplantation period is a very initial process of pregnancy when most women do not know that they are pregnant. In the last two decades, due to the increased use of *in vitro* fertilization, our knowledge on the early developmental events in the preimplantation and preorganogenetic human embryos expanded. In spite of that, most of our knowledge still comes from animal studies. Similarly in order to understand these early events in diabetic pregnancies, most studies are still carried out on diabetic animal models.

It is important to note that insulin and insulin-like growth factors (IGFs) seem to be essential for normal growth of the early embryo in the blastocyst stage as well as for the process of gastrulation.¹ Hence, it is not surprising that diabetes may interfere with early embryonic development.

Maternal diabetes in rodents influences embryonic and fetal development in a very similar manner to that of humans.² Hence, most studies discussed in this chapter were carried out on diabetic rodents or in *in vitro* models. We will describe the effects of maternal diabetes starting from the ovum, gradually continuing to later preimplantation stages, and then discuss the proposed mechanisms of action.

Changes in oocytes

Most studies on the effects of maternal diabetes on early pregnancy focused on the zygote, only few recent studies started to examine the oocytes.

In the developing oocyte, the surrounding granulosa cells support its growth and provide hormonal supplementation. There are several interactions between the oocyte and the granulosa cells such as paracrine signaling and gap junctional communication. These interactions are critical for the oocyte differentiation and growth.³

Chang et al.⁴ suggested that maternal diabetes adversely affects preovulatory oocyte maturation, oocyte development, and granulosa cell apoptosis in mice. Their main hypothesis was that reduction in paracrine communication between the granulosa cells and the oocyte in diabetic mice causes a maturational delay. Indeed, in mice with chronic hypoinsulinemia and hyperglycemia (Akita diabetic mice) or in mice with acute hyperglycemia and hypoinsulinemia (induced by streptozotocin [STZ] injection), the preovulatory follicles and oocytes were small with more apoptotic follicular cells in comparison with controls. In addition, there was a delay in meiotic maturation, upregulation in the expression of cell death signaling proteins, and a decrease in the expression level of key gap junction proteins such as connexin-43 that are necessary for communication.

Recently, Aktug et al.⁵ studied the morphology of 279 oocytes obtained from STZ-induced diabetic rats compared to 336 oocytes obtained from nondiabetic animals. They found a lower percentage of mature oocytes and a higher percentage of atretic and postmature oocytes among the diabetic rats compared to controls. In addition, a lower *in vitro* fertilization rate was observed among oocytes from diabetic animals and a decrease in the expression of beta-catenin and connexin gene family.

In conclusion

Maternal diabetes, as evidenced from the studies in mice and rats, may interrupt the normal communication of the oocyte and its surrounding cells increasing apoptosis, thus leading to abnormal development of the oocyte. This may lead to increased atretic and postmature oocytes and therefore to reduced fertilization ability. This might, if extrapolated to man, cause menstrual disturbances, reduced fertilization rate, different embryonic insults, or very early miscarriage, as indeed found in diabetic women.⁵

Zygote and morula

The mechanism of the developmental delay of the zygote is not clear. Several studies investigated the development of the zygote in diabetic rats. Diabetes was induced by ablation of the insulin-secreting islet cells by STZ. These studies showed delay in early developmental progression of the zygotes and reduced implantation rates.⁶ Other studies, carried out on embryos recovered from non obese diabetic (NOD) diabetic or nondiabetic mice 72 hours after fertilization, showed an increased percentage of embryos at the one-cell stage, as these embryos could not continue their normal dividing process.⁷ When these embryos were further cultured in the presence of high D-glucose concentrations, severe growth retardation was demonstrated. No impairment of growth was observed following culture in high L-glucose concentrations. Similar results were obtained when two-cell stage mouse embryos were obtained from nondiabetic mice but cultured on culture media containing high concentrations of D-glucose.⁸

Other studies have examined substrate utilization in the developing mouse embryos. Many zygotes that were incubated in high concentrations of glucose or lactate failed to progress to the two-cell stage.^{8,9} Moreover, it is known that mouse embryos begin to utilize glucose for several synthetic processes at the eight-cell stage,⁹ and therefore the stages of morula and early blastocysts are highly susceptible to high glucose concentrations.

It can be concluded that high glucose levels at the earliest developmental stages, starting from 1 to 2 cells, can influence the future embryonic development and may even stop cell division and growth.

Blastocyst

Leunda-Casi et al.¹⁰ examined how high levels of glucose influence the development of mouse blastocysts. Embryonic exposure to high levels of D-glucose for a short time impaired trophoblast differentiation, and the outgrowth of the trophoblast was increased. This effect was secondary to a deficiency in fibroblast growth factor-4 (FGF-4) protein in the inner cell mass (ICM). The addition of FGF-4 to the blastocysts pretreated with high glucose normalized trophoblastic growth. The authors conclude that FGF-4 is important in the normal differentiation of the trophoblast and that these observations could explain some of the morphological changes detected in the placentae of diabetic pregnancies.¹⁰

A comparison between blastocysts from STZ-induced diabetic to normal rats indicated that the former contained a lower number of cell nuclei in the ICM on day 5 postfertilization. The proportion of morulae versus blastocysts was also different from controls, as the diabetic animals had more embryos persisting in the morula stage in comparison with controls or with rats injected with subdiabetogenic doses of STZ, and hence not diabetic.¹¹ Treatment of the diabetic rats with insulin during the preimplantation period (day 1–6 of pregnancy) normalized embryonic growth and development.¹² These studies demonstrate that the embryonic

damage is due to the diabetes and not to the possible action of STZ. In the same line, other studies have shown that STZ-induced diabetic rats had a 15%–20% decrease in the total cell number of the ICM, a 20%–25% decrease in the implantation rate, and a similar reduction in the number of blastocysts.⁵ However, the implanted blastocysts seem to be normal, as their protein synthesis was similar to that of implanted blastocysts from nondiabetic animals.

In contrast to the reduction in the number of ICM cells, high glucose concentrations did not change the number of trophoblastic cells.⁵ Hinck et al.¹³ studied the differentiation of Rcho-1 rat trophoblastic cells into giant cells in a culture medium supplemented with different concentrations of glucose. High glucose concentrations increased the number of trophoblastic cells; their nuclei were smaller and contained more DNA compared to control cells. While the cells cultured in control culture media increased their progesterone secretion, the addition of high glucose concentrations inhibited that increase. Apoptosis was not increased with the addition of glucose. These morphological and physiological changes (reduction in progesterone secretion) could interfere with implantation and may possibly explain the increased rate of early abortions in man.

Thieme et al.¹ recovered rabbit blastocysts 6 days postcopulation. The rabbits were made diabetic by alloxan with postfeeding blood glucose level ranging between 14 and 25 mmol/L. In the diabetic animals, compared to nondiabetic ones, blastocyst development was delayed and no embryos reached the pregastrulation stage. The authors explain the growth and developmental delay of the diabetic blastocysts by the lack of insulin and IGF1 that are needed for normal embryonic development. They indeed found in vitro that insulin is required for Wnt3a, Wnt 4, and Brachyury gene expression and that, in blastocysts removed from diabetic rabbits at the pregastrulation stage, when only Wnt3a is normally expressed, the expression of this gene was significantly downregulated.

Cagnone et al.¹⁴ cultured in vitro fertilized bovine morulae in control and hyperglycemic culture medium and studied the gene expression profiles in the blastocyst stage. They found by microarray analysis differences in gene expression between the embryos cultured on hyperglycemic culture medium and controls. In the “diabetic” blastocysts, they observed overexpression of genes involved in metabolic control such as extracellular matrix signaling, calcium signaling, and energy metabolism. They also observed upregulation of HIF1 alpha signaling, a finding described by us also in early somite rat embryos cultured in diabetic culture medium.¹⁵ Hence, they have shown that hyperglycemia induces at the blastocyst stage significant epigenetic changes, similar to those described by several investigators during later developmental stages in “diabetic” embryos.

In conclusion

High glucose increases apoptosis of the ICM and may cause embryonic death. Reduction of insulin, such as in type 1 diabetes, may cause embryonic growth delay. Hyperglycemia-induced changes in gene expression can be observed already at that developmental stage. Trophoblastic cells are not diminished in number; on the contrary, their number may even increase.

In vitro studies on preimplantation embryos

1. *Culture in "diabetic" culture medium:* We cultured preimplantation mouse blastocysts for 72 hours in Roswell Park Memorial Institute (RPMI) medium with the addition of 10% fetal bovine serum and found 20%–24% of embryonic developmental arrest.¹⁶ Addition of high concentrations of glucose, acetoacetate, β -hydroxybutyrate, glucagon, and insulin were all embryotoxic, inducing a high percentage of embryonic death. However, while the concentrations of most substances were much higher than possibly found in diabetes, the embryotoxic glucose concentrations were only 300 mg%, concentrations often observed in diabetes. Moreover, a combination of β -hydroxybutyrate, acetoacetate, and glucose, in relatively low concentrations, was more embryotoxic than each of the substances individually. In addition, 50% serum from STZ-induced diabetic rats added to the culture medium caused 53% of embryonic developmental arrest, while 20% and 50% of rat and human control serum did not reduce the number of normally developing embryos.
2. *Culture in sera from diabetic pregnant women:* We cultured, in two sets of experiments,¹⁷ mouse embryos on RPMI culture medium with 30% or 50% serum obtained from women with pregestational diabetes (PGD) (type 1 or type 2) or gestational diabetes (GD), in comparison with similar concentrations of serum from nondiabetic women. The results are shown in Tables 40.1 and 40.2.

At first, we cultured 2–4-cell mouse embryos for up to 72 hours to the early blastocyst stage in 30% serum from pregnant women with PGD or with GD and found that a high proportion of these embryos stopped from further developing within 24–72 hours of culture (Table 40.1). The developmental stage of the living embryos was also reduced, but this reduction was significant only after 72 hours of culture (Table 40.1). When we cultured early blastocysts in 50% diabetic serum, about half of the blastocysts died within the first 48 hours of culture, but from that stage, all living embryos had spread on the Petri dish and continued to develop normally. Hence, the developmental stages of the living embryos were not different from that of controls (Table 40.2). There was a negative correlation between the degree of diabetic control and the extent of damage to the embryos. The sera from women with good control had less deleterious effects on the zygotes, morulae, or early blastocysts. Sera from women with GD were also less embryotoxic than sera from women with PGD.

These results imply that human diabetic serum may stop mouse morulae and/or early blastocysts from further development and retard the development of living morulae. However, these sera do not retard the development of living late blastocysts and do not interfere with their hatching. The developmental stage specificity of the hyperglycemia-induced injuries is apparently related to age-specific metabolic changes.

Table 40.1 Effects of 30% serum from diabetic pregnant women on the developmental stages of two- to four-cell stage mouse embryos cultured for 72 hours

Number of living embryos and their developmental stage			
Serum obtained from	At beginning	At 48 hours	At 72 hours
Control	2.0 $\pm$ 0.05 (195)	8.1 $\pm$ 1.0 (177)	10.5 $\pm$ 0.7 (173)
Type 1 diabetes	2.2 $\pm$ 0.4 (170)	7.0 $\pm$ 0.7 (159)	8.9 $\pm$ 0.7 ^a (128) ^a
Type 2 diabetes	2.3 $\pm$ 0.4 (128)	7.6 $\pm$ 0.8 (101)	9.2 $\pm$ 0.8 ^a (84) ^a
Gestational diabetes	2.1 $\pm$ 0.1 (215)	7.8 $\pm$ 1.2 (188)	9.3 $\pm$ 0.5 ^a (160)

Note: Values are mean $\pm$ SD (number of embryos).

^a Significantly lower than control, $p < 0.05$.

Table 40.2 Effects of 50% serum from diabetic pregnant women on the developmental stages of mouse blastocysts cultured for 72 hours

Number of living embryos and their developmental stage			
Serum obtained from	At beginning	At 48 hours	At 72 hours
Control	7.8 $\pm$ 0.6 (105)	10.5 $\pm$ 0.7 (98)	11.7 $\pm$ 0.7 (97)
Type 1 diabetes	7.6 $\pm$ 0.2 (144)	10.6 $\pm$ 0.7 (77) ^a	11.8 $\pm$ 0.1 (77) ^a
Type 2 diabetes	7.4 $\pm$ 0.5 (132)	10.6 $\pm$ 0.7 (63) ^a	11.8 $\pm$ 0.2 (62) ^a
Gestational diabetes	7.9 $\pm$ 0.5 (183)	10.6 $\pm$ 0.4 (125) ^a	11.9 $\pm$ 0.0 (123) ^a

Note: Values are mean $\pm$ SD (number of embryos).

^a Significantly lower than control, $p < 0.05$.

In summary

The observations in diabetic mice and rats show that maternal diabetes may damage early embryonic development. This might lead to early embryonic death and, if pertinent to the human situation, to very early miscarriage, even before pregnancy is clinically recognized. Whether in such preimplantations very early spontaneous abortions really occur in diabetic women, is currently unknown.

Spontaneous abortions in diabetic women

If the data in animal models are relevant to humans, it is expected that diabetic women will have an increased rate of early miscarriages. Indeed, most human studies observed increased rate of spontaneous abortions in women with PGD. For example, a retrospective sample of 164 pregnancies during 1956–1975 of 78 insulin-dependent diabetic women was examined in order to evaluate the risk of clinically recognizable spontaneous abortions in diabetic women in comparison with the normal population.¹⁸ This study was done before the policy of meticulous control of diabetes in pregnancy. The risk of spontaneous abortions among the diabetic females was almost double compared to the nondiabetic women. Later retrospective studies from 1980 to 2000 showed lower differences in the rate of spontaneous abortions between the diabetic and the nondiabetic women. Jovanovic et al.¹⁹ followed 389 diabetic and 429 nondiabetic pregnant women. They found that the mean pregnancy loss rates were 12% in diabetic and 13% in normal pregnancies. When they examined the glucose blood levels, they found that both nondiabetic and diabetic women had high glucose levels. However, the level of hyperglycemia tolerated in the diabetic pregnancies before reaching the threshold of fetal sensitivity was higher than that in nondiabetic pregnancies, implying maternal, placental, or fetal defenses to the stress of hyperglycemia.

It can be assumed that these significant differences are caused by the differences in the control of diabetes, and with improved glycemic control, the rate of spontaneous abortions is reduced. This is in accordance to the fact that serum from women with well-treated diabetes was less deleterious to mouse embryos in culture than serum from women with poorly controlled diabetes.¹⁷

Possible mechanisms of action of diabetes on the early embryo

Several mechanisms were shown to play a role in diabetes-induced early embryopathy in animals. Elucidation of these mechanisms of action may help to understand the human situation. We will, therefore, discuss these mechanisms mainly based on experimental animal models.

Apoptosis

Hyperglycemia induces excessive cell death in the ICM of rat blastocysts, which was characterized mainly by nuclear

fragmentation. It was shown that these cells contain a large amount of the clusterin transcripts, a gene associated with apoptosis. The overexpression of clusterin in blastocysts of STZ-induced diabetic rats indicates that these embryos may be affected by subtle disruptions in the expression pattern of critical developmental genes.²⁰ Similar to the previous study, blastocysts from diabetic rats and mice showed increased nuclear chromatin degradation in the ICM cells.^{21,22} These and other studies demonstrate that in preimplantation embryogenesis, hyperglycemia triggers increased apoptosis, especially at the blastocyst stage. Maternal hyperglycemia caused a decrease in the expression of facilitative glucose transporter genes such as GLUT1 (glucose transporter), GLUT2, and GLUT3, which was associated with the reduction in glucose transport to the embryo and a decrease in intraembryonic free glucose.²² This mechanism acts as a signal for cell death that triggers p53 activity. The hyperglycemia-induced cell death signal increases the expression of the proapoptotic protein BAX, which is a member of the Bcl-2 family.²² In addition, mRNA levels and protein expression of BAX were higher in blastocysts cultured in hyperglycemic culture medium or in blastocysts obtained from STZ-induced diabetic mice.²² In rat blastocysts in culture, the transcription of the Bcl-2 gene and the activity of the protein were also markedly increased in the presence of high glucose concentrations in the culture medium.²³ These events induced by hyperglycemia lead to the activation of caspases, to DNA fragmentation, and morphological changes consistent with apoptosis. This cascade (Figure 40.1), connecting the expression of Bcl-2 and/or BAX with cell death signals involving p53, suggests that the hyperglycemia induces embryonic hypoglycemia due to the decrease in the glucose

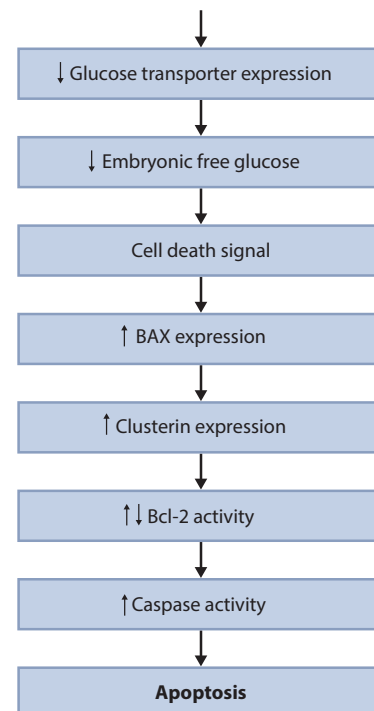


Figure 40.1 Hyperglycemia-induced apoptosis. (Modified from Keim, A.L. et al., *Mol. Reprod. Dev.*, 60, 214, 2001.)

transport expression and induces the p53 apoptotic cascade.^{22,23} It is important to note that P53 expression is necessary for the induction of apoptosis by hyperglycemia.²⁴

Of the different glucose transporters existing in the early embryo, GLUT8 was found to be one of the most important.²⁵ This transporter is regulated by insulin. During early differentiation of the mouse blastocyst, there is a significant increase in glucose demand, and insulin causes GLUT8 to move to the plasma membrane, thus increasing the uptake of glucose, which is then converted to lactic acid. It is presumed that, similar to other glucose transporters, hyperglycemia decreases GLUT8, hence reducing the uptake of glucose by the ICM, inducing cell death.

Mouse blastocysts, genetically BAX deficient (BAX $-/-$) obtained from diabetic dams, showed lower chromatin degradation and apoptosis than BAX-positive (BAX $+/+$) embryos. Furthermore, the embryos from the BAX-deficient diabetic mice had lower rates of malformations and resorption on day 14 of pregnancy.²² These data propose that increased apoptosis in the blastocysts might indicate future increased risk of early embryonic death or malformations, as observed in diabetic pregnancies.

The second apoptotic compound, Bcl-2, belongs to a family of proteins that operate in the effector phase of apoptosis and may either promote or inhibit apoptosis. An increase in the expression of the antiapoptotic Bcl-2 mRNA was observed in rat blastocysts that were cultured in 28 mM glucose for 24 hours, compared to blastocysts incubated in 6 mM glucose.²³ When the Bcl-2 expression was inhibited, using antisense oligodeoxynucleotide, there was an increase of chromatin degradation in blastocysts incubated in high glucose concentrations. The addition of specific inhibitors to caspase-3 and caspase-activated deoxyribonuclease prevented the degradation of rat blastocysts.²³

A third apoptotic compound, clusterin, a disulfide-linked heterodimeric protein associated with the clearance of cellular debris and apoptosis, was twice higher in embryos of diabetic rats than in control embryos.²¹ When rat and mouse blastocysts were incubated with high glucose concentrations, there was an increase in BAX, in clusterin expression, and in nuclear chromatin degradation.^{22,23}

It can be concluded that the significant loss of progenitor cells from the ICM makes the embryos more sensitive to later developmental deficiencies. Furthermore, it is known that normal embryogenesis can occur only if a sufficient number of functional ICM cells are available.²⁴ Increased apoptosis at this early stage of development may lead to spontaneous miscarriage or congenital malformations. Figure 40.1 summarizes the steps leading to diabetes induced increased apoptosis.

Oxidative stress and antioxidants

Many studies implied that the causes of diabetic embryopathy may be secondary cellular damage from overproduction of reactive oxygen species (ROS) or/and decreased antioxidant defense mechanism in the embryonic cells.^{17,26–28} The source of ROS is complex and nonspecific. The main

question is whether deranged oxidant antioxidant status can occur at this early stage of preimplantation embryonic development. We found that serum from diabetic women can induce oxidative stress in the mouse blastocysts,¹⁷ apparently in a way similar to that induced in postimplantation embryos.²⁶ This was evidenced by reduced concentrations of low-molecular-weight antioxidants (LMWA) such as glutathione and vitamins C and E. The preimplantation mouse embryos cultured in serum from diabetic pregnant women had a lower concentration of LMWA compared to embryos cultured in serum from nondiabetic women. It seems, therefore, that diabetic metabolic factors may induce embryotoxicity in preimplantation embryos through derangement of the antioxidant defense mechanism. Leunda-Casi et al.²⁸ found that hyperglycemia may increase ROS generation, and this might be one of the reasons for increased cell apoptosis as evidenced in this study by the TUNEL (terminal deoxynucleotidyl transferase dUTP Nick End Labeling) technique. Similar findings were reported by others in mouse zygote and blastocysts.²⁹ One of the key mediators that was suggested as the essence for apoptosis is hydrogen peroxide (H_2O_2). Violation of this balance by high glucose concentrations can cause massive cell damage, increase in apoptotic events, and defective embryonic development.³⁰ When there are high levels of glucose, they need to be degraded, and the result is a high production of ketone bodies and an increase in the production of ROS.

Fertilization and embryonic development take place in an environment of low oxygen tension. Oxygen tension is gradually increasing with advanced gestation, once placental is well established and maternal uterine arterioles are not obliterated by trophoblastic cells.^{27,28} Oxidative stress also seems to play an important role in the early phases of embryonic development, and hence antioxidants may play a significant role in preventing damage to the embryos.^{17,26,30–32}

ROS mediate their action through many of the proinflammatory cytokines. They can influence the oocyte, sperm, and embryos. During pregnancy, there are increased numbers of polymorphonuclear leukocytes that increase superoxide ions. This oxidative stress may regulate the expression of cytokine receptors in the placenta, cytotrophoblastic cells, vascular endothelial cells, and smooth muscle cells. In addition, several studies have also demonstrated the significant role of free radicals in placental function. Oxidative damage to the trophoblastic cells early in pregnancy or to the placenta during the establishment of its maternal circulation may also cause early pregnancy loss.^{30–32}

Growth factors and cytokines

Cytokines and growth factors play an active role in the normal implantation process. They also have important roles in the pathogenesis of diabetes-induced organ damage, and those that interrupt the reproductive tract are able to cause preimplantation embryopathy.^{33–35} There are only few reports that refer to cytokine expression in the diabetic uterus. IGF-2 synthesis is downregulated, and to the contrary,

tumor necrosis factor α (TNF- α) synthesis is upregulated around the implantation sites in diabetic female rats.^{36,37} Wu et al.^{38,39} showed a correlation between reduction in the concentrations of mRNA encoding IGF-2 and embryonic growth retardation 2 days after initiation of implantation in C57Bl/6J pregnant mice. However, later observations demonstrated that maternal diabetes did not affect the uterine IGF-1 expression. Detection of TNF- α revealed overexpression in the mRNA as well as in the protein concentrations in the preimplantation uterus of STZ-induced diabetic Wistar rats.³² The majority of TNF- α protein synthesis was located in the epithelium lining the uterine lumen. Despite normalization of glycemia by addition of insulin to the diabetic animals, it did not prevent the overproduction of TNF- α in the uterus.³⁷ Incubation of rat and mouse uterine cells in different glucose concentrations induced the stimulation of TNF- α secretion in uterine epithelial cells, apparently mediating the release of other cytokines, i.e., interleukin 1 β —from the sub-epithelial population of macrophages after their direct activation by hyperglycemia. There is evidence that high levels of TNF- α in utero can be harmful to the embryonic development at the implantation phase. Embryos exposed to high levels of TNF- α and surviving to term were significantly smaller than control embryos.^{34–40} Mouse embryonic stem cells indicate that TNF- α inhibits cell proliferation in the ICM lineage and decreased their differentiation potential.³⁵ Further evidence for the hypothesis that TNF- α contributes to the harmful influence of maternal diabetes on preimplantation development was found in blastocysts from Wistar rats. Culture medium was produced from normal and diabetic uterine cells; the blastocysts of Wistar rats incubated in these media showed diminished growth in the diabetic medium, but improved significantly (not completely) by pre-treating the blastocysts with antisense oligonucleotide that blocked the embryonic TNF- α receptors.⁴⁰

To conclude, there is an increased secretion of TNF- α in diabetic rats and mice at the preimplantation period that may harm the embryos, interfering with normal embryonic growth. A similar mechanism may be responsible for the increased risk of early embryonic loss in diabetic women.

Metabolic factors

Glucose metabolism

Glucose supplement in mouse blastocysts can be provided by the glucose transporters (i.e., GLUT1, GLUT8), by passive diffusion, and by an active transport system.^{24,41,42} In human and mouse blastocysts, the uptake of deoxyglucose is very active, and its concentrations in the mouse embryos were found to be 30 times higher than in the culture medium.⁴² This transport was blocked by cytochalasin B but not by substances that usually block the active transport of glucose in the gut or kidney, emphasizing that this mechanism is unique to the early developing embryo.

Suppression of GLUT1 in preimplantation embryos by antisense GLUT1 is known to produce ICM apoptosis, in a way similar to high glucose concentrations. In addition, in the GLUT1 transporter-deficient mouse, the embryos and

fetuses were found to exhibit the same damage and anomalies as observed in the offspring of diabetic animals,³⁹ further demonstrating the importance of glucose transport to normal early embryonic development.

Downregulation of GLUT1 mRNA and protein expression in mouse trophoblasts and in human term placental trophoblasts^{40–42} were observed after exposure to high glucose concentrations. It has therefore been suggested that the glucose transporter is regulated in the placenta by glucose and that, as a protective mechanism for the embryo, the transporter is being moved from the cell surface into an intracellular position, thus decreasing glucose uptake in hyperglycemia.^{43–46} This mechanism seems to protect the embryo from the toxic effects of high glucose concentrations.

Nitric oxide and prostaglandins

In the preimplantation period, when the trophoblastic cells penetrate the decidua, there is an increase in vascular permeability and other inflammation-like changes. This increase in vascular permeability is related to vasoactive agents like nitric oxide (NO) and prostaglandins (PGs), as both are associated with increased vascular permeability, vasodilation, and increased blood flow in the uterus. At the beginning of implantation in the rat uterus, there is an increase in the NO synthase activity, synthesizing more NO, and in the production of PGE, PGF2 α , and PGI2.^{47,48} Moreover, when the synthesis of NO or PGs in the uterus is blocked, there is a decrease in the number of implanted rat embryos. During preimplantation, there is an oversensitivity to metabolic disturbances, and the external environment can easily affect embryonic development. Novaro et al.⁴⁸ studied the uterine synthesis and temporal pattern of two vasoactive agents, NO and PGE, both modulating the implantation process in rats with non-insulin-dependent diabetes mellitus, and found that the activity of NO synthase in the rat uterus and the production of PGE were increased in diabetes. In addition, the temporal profile of their activity was different from the control animals, and the number of implanted embryos was reduced. However, the implantation rate was not different between the diabetic and control animals. While the NO increase was observed in different tissues, PGE production was located at the implantation sites and remained high after the implantation. The authors suggest that the increase of PGE synthesis in diabetic uterine tissue is a secondary effect. First, there is an increase in NO production; NO regulates the synthesis of PGs; together they have a positive influence on glucose metabolism and on the process of vasodilatation in the uterus. The rate and timing of the beginning of implantation are not altered by diabetes, but diabetes may damage the early blastocysts, reducing the number of embryos that are able to implant normally.⁴⁸

Epigenetic changes

Many studies on embryos, fetuses, and placentae from diabetic animals have demonstrated a variety of epigenetic changes, especially changes in gene expression and in DNA

methylation induced by diabetic maternal environment.^{15,49} Several recent studies have shown that the changes in gene expression can already be observed at the earliest stages of embryonic development.^{1,5,14,50} In spite of the fact that these epigenetic changes (i.e., modifications of histones and DNA methylation) occur very early in development, many of them persist and can have transgenerational effects.⁵⁰ Hence, the different epigenetic changes observed in the early embryos might be responsible for many of the long-term and transgenerational effects commonly found in the offspring of diabetic mothers.

Effects on male fertility

Studies suggest that sexual dysfunction is frequently associated with diabetes in men and in experimental animals.⁵¹ Many of these problems result from diabetes-induced changes in the vascular system as well as in the peripheral and central nervous system that are related to changes in endocrine function.⁵² Studies on different diabetic male animals have documented abnormalities in testicular function and spermatogenesis.⁵³ Recently, Aktug et al.⁵ analyzed sperm from STZ-induced diabetic rats compared to nondiabetic animals. While the sperm number in the diabetic rats was markedly reduced, there was no difference in sperm abnormalities. In addition, studies demonstrated a reduction in the activity of ATPases and phosphatases in the epidermis and in spermatozoa.⁵⁴ Impotence, infertility, and retrograde ejaculation have been described in diabetic men, but the etiology remains unclear. The reduction in the

fertility of men with long-standing diabetes, by affecting spermatogenesis, seems to be similar to the effects of diabetes on the ova.

Conclusions

As there are practically no data in man except for reduced fertility and increased spontaneous abortions in diabetics, most of the research was done on animal models. A direct extrapolation of these studies to man must be with great caution, as it may lead to wrong conclusions. In addition, in most in vivo animal studies, diabetes was induced by ablation of insulin production, and it is possible that some of the results stem from how diabetes develops. However, many of the results were obtained also in vitro, including studies on human diabetic serum that served as culture medium, strengthening the simulation to man. There is a need for human additional studies to verify the different proposed mechanisms of diabetic-induced early embryopathy.

To summarize

Glucose blood levels can influence most processes related to oocyte maturation, fertilization, and early embryonic development. Good glycemic control in diabetic women, even before pregnancy is diagnosed, can decrease or possibly prevent most of these effects that, if not prevented, may have long-term consequences on early and late embryonic development.

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41 Postimplantation diabetic embryopathy

Ulf J. Eriksson and Parri Wentzel

Introduction

Despite increased clinical efforts to improve glycemic control during diabetic pregnancy, the rate of congenital malformations remains increased in studies of type 1^{1–12} and type 2 gestational diabetes,^{7–16} whereas the situation in GDM pregnancies remains controversial, the consensus leaning toward no, or marginally increased, occurrence of congenital malformations.^{13,17–24} This marginal incidence of congenital malformations may be related to the presence of undiagnosed type 2 diabetic women among women with diagnosed gestational diabetes (Table 41.1).

In recent studies, the occurrence of congenital malformations was estimated to 4%–6% in type 1 diabetic pregnancy^{8–10,12} and to 3%–5% in type 2 diabetic pregnancy.^{8–10,12} In two recent large meta-studies, it was found that the malformation rates in type 1 diabetic pregnancy did not differ from that of type 2 diabetic pregnancy^{25,26}; both rates were estimated to be around 5%–6%. The similar rates of malformation may relate to the increased age and concomitant adiposity in type 2 diabetic women, both of which may increase the incidence in this group.^{27–29}

The cell biological reason for the teratogenic effect of the diabetic state is not known. However, both environmental factors (maternal diabetic state and intrauterine conditions) and genetic predisposition seem to be of importance in diabetic embryopathy, i.e., this is an environment–gene interaction situation. The congenital malformations are likely to be induced in early gestation,^{30–32} and the risk of giving birth to a child with a malformation is increased by an increased degree of maternal dysregulation.^{33–36}

It has been suggested that the absence of a specific malformation pattern for diabetic embryopathy signals the presence of several teratological factors and mechanisms in diabetic pregnancy.³⁷ Likewise, the number of different teratogenic agents identified would indicate that diabetic embryopathy is of complex etiology.^{38–40} In the following, we will review the various etiological suggestions for diabetic embryopathy, in order to be able to present a reasonable overview of the major teratological pathway(s) and, consequently, to be able

to predict the possible future means of (prophylactic) antiteratological treatment of diabetic pregnancy.

Several reviews have recently characterized varied aspects of the complex teratological etiology of diabetic pregnancy^{41–46} and also compared diabetic teratogenesis with other teratogenic conditions.⁴⁷

First line of teratogenesis: Diabetes-induced alterations of maternal metabolites/nutrients

Several teratological factors in maternal serum have been suggested, often from clinical experience, and have been subsequently characterized in various experimental systems. The maternal teratogenic factors most often indicated are hyperglycemia and hyperketonemia. Also, alterations in maternal triglycerides/fatty acid and (branched-chain) amino acid levels have been suggested to have teratogenic roles, based on data from experimental studies (Table 41.2).

Glucose

An increased level of glucose (Figure 41.1) is the hallmark of the diabetic state, and there is ample clinical evidence that increased glucose/HbA1c levels correlate with increased risk of congenital malformation in the offspring.^{31–34,36,48–50} In experimental studies, the same correlation between increased serum glucose levels and increased risk for fetal malformations has been demonstrated in diabetic rodents.^{51–87} In addition, injections of glucose to pregnant, nondiabetic, animals have also yielded teratological effects.^{88,89} Furthermore, in vitro culture of rodent embryos in increased glucose concentrations,^{59,68,75,90–106} as well as in diabetic serum,^{39,40,94,107–114} yielded disturbed development.

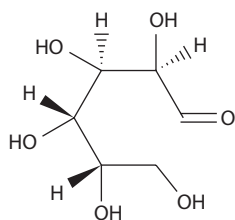
The alleged teratological effect of hyperglycemia is likely to be correlated with the metabolism of glucose, since exposure to L-glucose in vitro has no negative developmental effect.⁹⁰ Increased embryonic uptake of glucose by existing,¹¹⁵ often upregulated,^{116,117} glucose transporters

Table 41.1 Malformation rates

Type 1 DM—5%–6% congenital malformation
Type 2 DM—5%–6% congenital malformation
GDM—Background rate of congenital malformation

Table 41.2 First line teratogens

Glucose—Major teratogen; hyperglycemia correlates with congenital malformation risk
Ketone bodies—Teratogenic in experimental studies
Triglycerides/fatty acids—Associated with increased malformation rate in experimental studies
Branched-chain amino acids—Associated with increased malformation rate in experimental studies

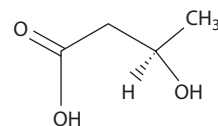
**Figure 41.1** Glucose.

also seems to be necessary for the teratogenic effect. The increased influx of glucose would yield increased glycolytic flux, as well as increased mitochondrial activity of the citric acid cycle and enhanced oxidative phosphorylation. Several consequences of increased glucose metabolism have been suggested,¹¹⁸ where increased mitochondrial production of superoxide may possess the most pronounced teratogenic potential. However, increased sorbitol production, increased hexose monophosphate shunt activity, reactive oxygen species (ROS)-mediated inhibition of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and increased formation of reactive alpha-oxoaldehydes may also play roles in diabetes-induced embryonic dysmorphogenesis. In addition, increased formation of advanced glycosylation end products (AGEs) and decreased intracellular availability of inositol and arachidonic acid (and its products, the prostaglandins) are suspected players in the teratogenic drama of diabetic pregnancy.

Of note, the preimplantation embryo follows another route toward maldevelopment, since a diabetes-induced decrease of the inner cell mass^{66,119} is likely to be induced by hypoglycemia, due to the downregulation of glucose transporters in the blastocyst, leading to decreased intraembryonic glucose levels^{120–122} and enhanced apoptosis.^{119,123}

Ketone bodies

The ketone bodies are synthesized in increased amounts in the (maternal) liver in response to the diabetic state. The two

**Figure 41.2** β -Hydroxybutyrate.

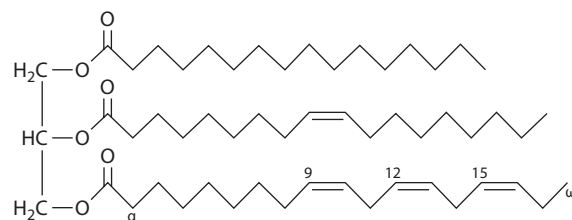
major compounds, beta-hydroxybutyrate (Figure 41.2) and acetoacetate, traverse the placenta¹²⁴ and are utilized as a substrate (acetoacetyl-CoA) in the embryonic mitochondria. There is experimental evidence of the teratogenic role of other diabetes-associated metabolites than increased glucose concentration, thus serum from diabetic rats with normalized glucose levels is still teratogenic in *in vitro* cultures,^{40,113} and the direct exposure to increased ketone body levels *in vitro* yields disturbed development in cultured rodent embryos.^{125–132} The mechanism for ketone body teratogenesis should also include metabolism of the compounds.¹³³

Triglycerides/fatty acids

The maternal non esterified fatty acids (NEFA) and fatty acids from (hydrolyzed) triglycerides (Figure 41.3) cross the placenta and reach the embryo and fetus.^{124,134} Preimplantation rabbit embryos exposed to a diabetic environment *in vivo* or high glucose and lipid concentration *in vitro* have increased intracellular lipid accumulation and enhanced expression of key genes for lipid storage, fatty acid transport, metabolism, and lipogenesis.¹³⁵ Increased levels of triglycerides/fatty acids^{72,113,136} have been associated with congenital malformations in experimental diabetic pregnancy. In fact, culture of rodent embryos in serum of rats given a high-fat diet yields developmental defects (Wentzel et al., manuscript). The likely mechanism would be associated with the beta-oxidation of the fatty acids, leading to increased flux in the citric acid cycle and enhanced oxidative phosphorylation.

Branched-chain amino acids

Branched-chain amino acids are transported to the embryo/fetus¹³⁷ and used as fuel and for protein synthesis. This class of amino acids is increased in the serum of diabetic individuals, as well as in the serum of diabetic pregnant rats, where this increase correlates with embryo dysmorphogenesis.^{72,138} *In vitro* culture with the leucine analogue (Figure 41.4), alpha-ketoisocaproic acid (KIC), yields disturbed development in rat embryos.¹⁰¹ The branched-chain amino acids are metabolized to citric acid metabolites (acetyl-CoA or succinyl-CoA) and utilized for oxidative phosphorylation.

**Figure 41.3** Triglyceride.

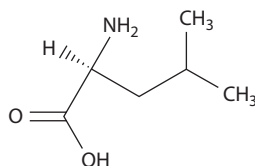


Figure 41.4 Leucine.

Combination effect

Culture of rat embryos in a combination of subteratogenic levels of glucose, beta-hydroxybutyrate, and KIC yields disturbed in vitro embryonic development, thereby supporting the notion of a synergistic relationship between the diabetes-associated metabolites.¹⁰¹

All of the proximal teratogens identified can serve as metabolic substrates in the embryo (and mother), and the most prominent teratogen, glucose, has the most complex metabolism involving glycolysis. Furthermore, the metabolic pathways of the primary (maternal) teratogens converge at the citric acid cycle and oxidative phosphorylation in the mitochondrion, which has led to the speculation that an overactivity of the oxidative phosphorylation pathway may be at the core of diabetic teratogenicity (Figure 41.5).

Second line of teratogenesis: Diabetes-induced alterations of fetal metabolites/nutrients

Major teratogenic processes in embryonic tissues so far identified include alterations of signaling systems such as the metabolism of inositol,^{92,97,98,139–141} sorbitol,^{92,98,140,142,143} arachidonic acid/prostaglandins,^{84,97,105,144–148} and folate (Table 41.3).^{149,150}

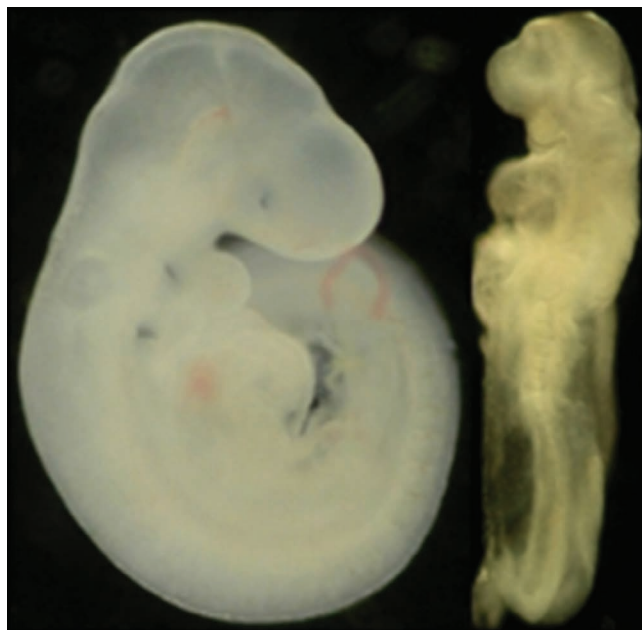


Figure 41.5 Day 11 embryos from normal (left) and diabetic (right) rats; the latter is malformed (growth retarded, failed rotation, and NTD).

Table 41.3 Second line teratogens

Inositol—Deficiency is teratogenic in experimental studies
Sorbitol—Accumulation parallel to hyperglycemia-induced malformations
Arachidonic acid/prostaglandins—Alterations are teratogenic in experimental studies
Folate—Deficiency is teratogenic in experimental studies

Inositol

Inositol (Figure 41.6) is taken up by cells via a saturable mechanism, which is inhibitable by glucose, in preimplantation embryos,¹⁵¹ as well as in adult individuals. This has led to the speculation that glucose-induced inositol deficiency may be an integral part of the pathogenesis of diabetic complications,¹⁵² as well as of diabetic embryopathy.⁹² The immediate effect of lowered inositol concentration would be decreased levels of the phosphoinositides (PI, PIP, and PIP₂) and their products in the embryonic tissue.¹⁰⁰ A lack of PIP₂ would subsequently yield less IP₃ and diacylglycerol (DAG), both of which are stimulators of protein kinase C (PKC) activity. A lowered PKC activity would exert a number of effects, including lowered activity of phospholipase A₂,¹⁵³ which would subsequently diminish the availability of free arachidonic acid and thereby hamper the production and metabolism of prostaglandins, as discussed later.

Rat embryos cultured in inositol-depleted serum develop neural tube defects (NTDs),¹⁵⁴ which demonstrates the teratogenic capacity of inositol deficiency. In addition, when curly tail mouse embryos, who have a predisposition for developing folate-resistant NTDs, are cultured in inositol-depleted serum, their NTD rate increases further.¹⁵⁵ If the inositol-depleted culture medium is successively supplemented with inositol, the NTD rate in the curly tail embryos decreases proportionally¹⁵⁵ and results in a lower NTD rate than in nontreated curly tail embryos.¹⁵⁶ Also, administering *myo*-inositol or *D-chiro*-inositol to curly tail mice, both in vivo and in vitro, diminishes the NTD/spina bifida rate.¹⁵⁷

High glucose concentration in vitro causes decreased levels of inositol in the embryo due to impaired uptake,¹⁴¹ yielding an embryonic deficiency of inositol^{92,100,140,158} concomitant with an increased rate of embryonic dysmorphogenesis. Supplementation of *myo*-inositol to high glucose-cultured embryos,^{97,98,139} or dietary addition to diabetic pregnant rodents,^{67,158–160} diminishes both the

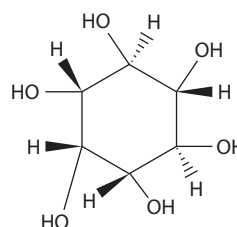


Figure 41.6 Inositol.

inositol deficiency and the rate of embryonic maldevelopment. Furthermore, adding the inositol uptake inhibitor *scyllo*-inositol to the culture medium of rodent embryos causes similar changes as excess glucose to the embryos, i.e., both inositol deficiency and embryonic maldevelopment.^{100,161,162} In addition, similarly to the glucose-induced damage, both inositol deficiency and embryo maldevelopment caused by *scyllo*-inositol can be diminished by the addition of inositol to the culture medium.^{100,161,162} These findings identify inositol deficiency as a likely component of diabetic teratogenesis.¹⁶³

However, the addition of antioxidants diminishes both glucose-induced and *scyllo*-inositol-induced embryonic dysmorphogenesis in vitro^{114,162}; therefore inositol deficiency appears to induce embryonic oxidative stress, which, in turn, affects embryonic development; see the following.

Sorbitol

Sorbitol (Figure 41.7) is formed from glucose with the addition of aldose reductase (AR) and further metabolized to fructose by sorbitol dehydrogenase. In the presence of increased intracellular levels of free, nonphosphorylated glucose, an increased amount of sorbitol is formed, and accumulated, due to the low capacity of sorbitol dehydrogenase. This accumulation of sorbitol is likely to be part of the pathogenesis of diabetic complications,^{164,165} e.g., neuropathy, nephropathy,¹⁶⁶ and retinopathy, but it has also been suggested to have a role in diabetic embryopathy.

Exposure to a diabetic environment yields enhanced embryonic formation of sorbitol.^{92,98,140,142,143} Several studies of AR inhibitors in pregnant diabetic animals have managed to lower the increased sorbitol levels, however, without diminishing the increased malformation rates.^{92,98,167} However, in a recent in vitro study of cultured neural stem cells (NSCs), it was found that high glucose induced ROS production, decreased NSC viability and proliferation, and enhanced mRNA expression of AR.¹⁶⁸ Administration of fidarestat, an AR inhibitor, decreased the oxidative stress, restored cell viability and proliferation, and reduced apoptotic cell death in NSCs exposed to high glucose levels, suggesting that the activation of the polyol pathway may play a role in the induction of oxidative stress resulting in disturbed development of the neural tube in embryos of pregnant animals with diabetes.¹⁶⁸

Taken together, the experimental data provide only a limited support for the role of sorbitol accumulation in diabetic embryopathy, and it appears, at the present state of the research, to be a side phenomenon to the teratogenic pathway.

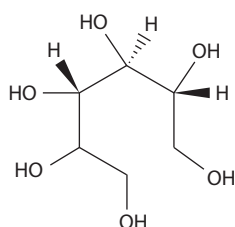


Figure 41.7 Sorbitol.

Arachidonic acid/prostaglandins

Arachidonic acid (Figure 41.8) is a polyunsaturated fatty acid present in the phospholipids of cell membranes. The metabolism of arachidonic acid and its products, the prostaglandins, is crucial for cellular life. In particular, arachidonic acid is involved in cellular signaling as a lipid second messenger.

Disturbed metabolism of arachidonic acid and prostaglandins has been found in previous studies of experimental diabetic pregnancy. Intraperitoneal injections of arachidonic acid to pregnant diabetic rats diminished the rate of neural tube damage,⁵⁹ as did enriching the diet of the pregnant diabetic rats with arachidonic acid.^{160,169,170} The addition of arachidonic acid to the culture medium was shown to block the embryonic dysmorphogenesis elicited by high glucose concentration,^{59,93,105} Addition of PGE2 to the culture medium also blocked glucose-induced teratogenicity in vitro,^{97,105} as well as maldevelopment of embryos cultured in diabetic serum.¹¹¹ Measurements of PGE2 have indicated that this prostaglandin is decreased in embryos of diabetic rodents during neural tube closure,^{147,171} in high glucose-cultured embryos,¹⁴⁷ as well as in the yolk sac of embryos of diabetic women.¹⁷²

Previous studies have shown that the uptake of arachidonic acid by embryonic yolk sacs is increased in a hyperglycemic environment.¹⁴⁵ This finding would preclude an uptake deficiency of arachidonic acid in the conceptus of diabetic pregnancy, a result supported by the demonstration of unchanged concentration of arachidonic acid in the membranes of high glucose-cultured embryos in vitro.¹⁷³ Measurements in day 12 embryos, however, indicated a decreased arachidonic acid concentration in offspring from diabetic rats.¹⁵⁸ Disturbances in the availability or metabolism of arachidonic acid affect the synthesis of prostaglandins. Alteration in the activity of the rate-limiting enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H2, may be of major importance. There are two isoforms of COX, COX-1 (constitutive) and COX-2 (inducible). A glucose-induced downregulation of the gene expression of COX-2 and a GSH-dependent decrease of the conversion of the precursor PGH2 to PGE2 (PGE synthase) have been demonstrated.¹⁴⁷ Thus, the PGE2 concentration of day 10 embryos and membranes was decreased after exposure to high glucose in vitro or diabetes in vivo. In vitro addition of *N*-acetylcysteine (NAC) to high-glucose cultures

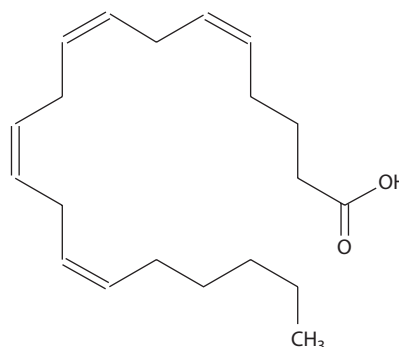


Figure 41.8 Arachidonic acid.

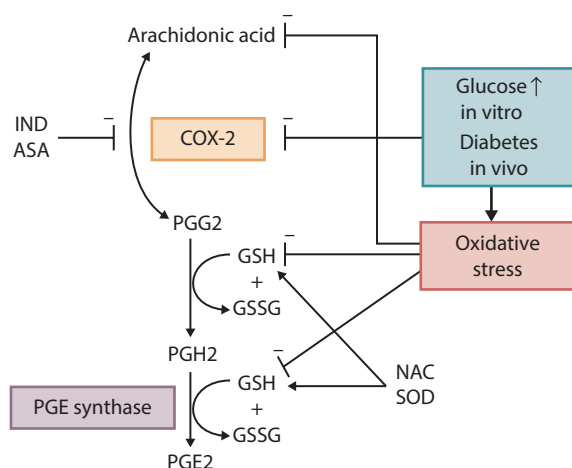


Figure 41.9 Schematic outline of arachidonic acid teratogenesis.

restored the PGE2 concentration.¹⁴⁷ Hyperglycemia-/diabetes-induced downregulation of embryonic COX-2 gene expression may be an early event in diabetic embryopathy, leading to lowered PGE2 levels and dysmorphogenesis, presumably because this pathway plays an important role in neural tube development. Antioxidant treatment does not prevent the decrease in COX-2 mRNA levels but restores PGE2 concentrations, suggesting that diabetes-induced oxidative stress aggravates the loss of COX-2 activity. From these data, it may be concluded that decreased availability of arachidonic acid and the resulting decrease in several prostaglandins, in particular PGE2, are likely to be involved in the teratogenicity of diabetic pregnancy.¹⁷⁰

Other studies have shown that a diabetes-like environment decreases embryonic PGE2 concentration^{146,147,171} in embryonic tissues (Figure 41.9). Affected arachidonic acid metabolism disturbs prostaglandins and embryogenesis.⁴¹

Folate

Vitamin B9 (folate) has to be supplied via the diet and is essential for numerous cellular functions, such as to synthesize, repair, and methylate DNA, as well as to act as a cofactor in several biological reactions. It is therefore needed for rapid cell division and growth and has an important role in the closure of the neural tube. Folic acid (Figure 41.10) is a

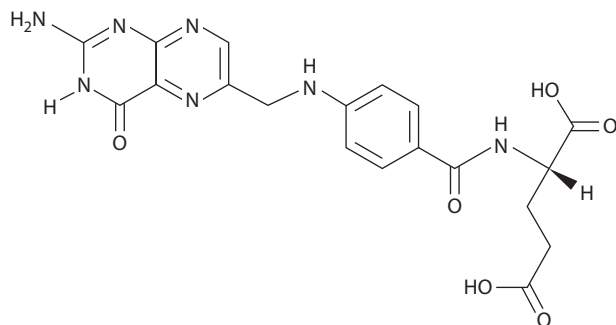


Figure 41.10 Folic acid.

synthetic form of folate, which is stable and often used in food fortification. The 5-methyltetrahydrofolate is the active form of folate and plays a substantial role in metabolism, particular in rapidly proliferating cells, in both pyrimidine and purine synthesis and the formation of methionine from homocysteine and the conversion of phenylalanine to tyrosine.

Functional deficiency of folate during early pregnancy may result in NTDs, such as spina bifida, and consequently, administration of folic acid in the periconceptional period protects the offspring from developing NTDs.^{174–176} Fortification of the U.S. diet with folic acid in 1996 coincided with a reduced incidence of NTDs from 0.38 to 0.31 per 1000 live births.¹⁷⁷ In Canada, folic acid fortification of all cereal grain products started in January 1998, and the NTD incidence has been compared before and after the fortification. In the province of Ontario (336,963 births), the NTD prevalence decreased from 1.13 to 0.58 per 1000 live births,¹⁷⁸ and in whole Canada (1.9 million births), the decrease was from 1.58 to 0.86 per 1000 live births.¹⁷⁹

It has been suggested that disturbed folate metabolism is involved in diabetic teratogenesis. This is based on the increased incidence of NTD in diabetic pregnancy^{180,181} compared with nondiabetic pregnancy. A recent report from the U.S. National Birth Defect Prevention Study (1997–2004) suggested that a periconceptional intake of vitamins or supplements that contain folic acid may diminish the risk for NTDs in diabetic pregnancy,¹⁸² which is in line with a previous report from the Atlanta Birth Defects Case-Control Study where diabetic women who took multivitamins during the periconceptional period had diminished the risk of having a baby with a birth defect.¹⁸³ Similarly, in a study from northern England, diabetic women with no folate supplement before pregnancy had a doubled risk for a baby with a birth defect.¹¹ However, after adjustment for HbA1c, the statistical significance of this finding disappeared. Also, a recent Dutch study reported that periconceptional folic acid supplement decreases the risk for congenital cardiac malformation,¹⁸⁴ indicating that folate deficiency may hamper embryonic development in other organs than the neural tube.

In experimental studies of folic acid administration to rat embryos exposed to diabetes in vivo and hyperglycemia in vitro, it was shown that folic acid treatment increased folic acid concentration in the embryos and almost completely abolished diabetes-/glucose-induced dysmorphogenesis, i.e., both the growth retardation and somatic maldevelopment in the embryos.^{149,150} This beneficial effect of folic acid treatment was thus present both in vivo and in vitro. The possibility that the cellular uptake of folate may be hampered by a diabetic/hyperglycemic environment was inspired by earlier studies where *Folbp1*^{−/−} embryos display severe morphogenetic abnormalities and die in utero by embryonic day 10.¹⁸⁵ The cellular uptake of 5-methyltetrahydrofolate is mediated by clusters of membrane-bound transport proteins (folbps). In both in vivo and in vitro studies of embryos, the *folbp* gene expression was decreased on day 10 and supplementation of folic acid normalized the embryonic mRNA expression of *folbp*.¹⁴⁹

In subsequent experiment, it was reported that folic acid supplementation to pregnant diabetic mice reduced the malformation rate (NTD, cardiovascular and skeletal anomalies) in fetuses.¹⁸⁶ Also, folic acid supplementation, in conjunction with safflower oil, decreased resorptions and malformations in diabetic rats.¹⁸⁷ It was also reported that folic acid administration diminishes apoptosis and differentiation of embryonic stem cells (ESCs) exposed to diabetes¹⁸⁸; however, in further experiments it was found that folic acid administration may also change the differentiation of neural progenitor cells in embryos of diabetic mice,¹⁸⁹ an observation that will need further investigation.

The experimental reports suggest that folic acid has a marked antiteratogenic effect on embryonic development in a diabetic environment.

Diabetes-induced fetal processes with suspected teratological impact

Several enzyme systems have been reported as disturbed in the offspring of diabetic animals, and, consequently, have been assumed to be part of the teratogenic process. The two most often reported are varied activation/inhibition of PKC isoforms^{162,190–195} and activation of c-Jun N-terminal kinases (JNKs) (Table 41.4).^{196–200}

Protein kinase C activity

PKC is a family of protein kinase enzymes that phosphorylates hydroxyl groups of serine and threonine amino acids in target proteins. PKC enzymes are activated by increased concentration of DAG, or calcium ions (Ca^{2+}). The PKC family consists of 15 isoenzymes in humans. They are divided into three subfamilies, based on their second messenger requirements: conventional (or classical), novel, and atypical. Conventional (c)PKCs contain the isoforms α , βI , βII , and γ . These require Ca^{2+} , DAG, and a phospholipid such as phosphatidylserine for activation. Novel (n)PKCs include the δ , ϵ , η , and θ isoforms and require DAG, but do not require Ca^{2+} for activation. Thus, conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase C. On the other hand, atypical (a)PKCs (including protein kinase ζ and ι/λ isoforms) require neither Ca^{2+} nor DAG for activation.

Investigations of a possible teratological role for PKC in diabetic pregnancy initially showed that nonspecific inhibition of PKC activity in cultured mouse embryos causes malformations and growth retardation,²⁰¹ and that addition of a nonspecific PKC inhibitor to high glucose–cultured

rat embryos does not block dysmorphogenesis.¹⁶² In subsequent work, it was shown that a diabetic environment *in vivo* caused a general increase in PKC activity, as well as increased DAG levels, concomitant with disturbed embryogenesis.¹⁹⁰ A detailed study of the activity of individual PKC isoenzymes in embryos of diabetic rats showed that PKC- α , PKC- βI , PKC- γ , PKC- δ , and PKC- ζ were increased.¹⁹¹ In addition, the PKC- γ and PKC- δ activities were further increased in malformed embryos.¹⁹¹

It has been reported that PKC signaling is associated with apoptosis, especially the isoforms PKC- δ ²⁰² and PKC- ζ .²⁰³ It has further been suggested that PKC- δ is involved in stabilizing p53 proteins²⁰⁴ and that it is related to ROS production,²⁰⁵ both of which would ultimately lead to apoptotic cell death. Since enhanced apoptosis is a feature of diabetic embryopathy (see later), one study used addition of specific inhibitors of PKC- δ and PKC- ζ to high-glucose culture medium and found diminished dysmorphogenesis.¹⁹² In a subsequent study with specific inhibitors of PKC- α , PKC- βII , and PKC- δ added to the high-glucose culture medium, it was shown that all of these inhibitors diminish embryonic dysmorphogenesis and decrease the glucose-enhanced activity of their respective PKC isoform.¹⁹³ In a subsequent study, inhibition of PKC- βII in high glucose–cultured mouse embryos diminished the rate of NTD and also decreased several glucose-induced embryonic effects, such as activation of Bid, caspase 8 and 3, and cytochrome C release from mitochondria.¹⁹⁴ Furthermore, in a recent study, female mice heterozygous for PKC- δ ($\text{pkc}\delta^{+/-}$) were made diabetic with streptozotocin (SZ) and mated with heterozygous males. The NTD rate in the diabetes-exposed homozygous ($\text{pkc}\delta^{-/-}$) embryos was markedly diminished compared with the rate of diabetes-exposed wild-type ($\text{pkc}\delta^{+/+}$) embryos.¹⁹⁵ Also, the diabetes-exposed $\text{pkc}\delta^{-/-}$ embryos had lower markers of oxidative stress, endoplasmic reticulum (ER) stress, as well as normalized expression of phosphorylated JNK (p-JNK).¹⁹⁵

These findings implicate PKC activity changes in diabetic embryopathy; however, the exact relationships between maternal diabetes, embryonic PKC isoforms activity, and embryonic developmental disturbances will be further investigated.

JNK activation

The family of JNKs has three isoforms, JNK1, JNK2, and JNK3, where JNK1 and JNK2 are found in all cells and tissues and JNK3 is found in the brain, heart, and testes. JNK is activated by several stress stimuli, e.g., changes in levels of ROS, ultraviolet radiation, inflammatory signals, and protein synthesis inhibitors. JNK phosphorylates and thereby modifies the activity of several mitochondrial and nuclear proteins. Downstream molecules that are activated by JNK include c-Jun and p53. By activating and inhibiting other cellular proteins, JNK thus regulates cell growth, differentiation, survival, and apoptosis.

Support for the notion that embryonic activation of JNK enzymes may be a constituent of diabetic embryopathy was initially found in the studies of embryos of diabetic

Table 41.4 Suspected processes

PKC activity—Alterations in activities correlate with malformations in experimental studies
JNK activity—Increased activity correlates with malformation in experimental studies

rats where the malformed embryos had increased yolk sac levels of p-JNK1/2 and decreased levels of phosphorylated ERK1/2 (p-ERK1/2) compared with yolk sacs of nonmalformed embryos from diabetic rats and from normal control embryos.^{196,197} In later work, this finding has been confirmed and expanded.²⁰⁶ Thus, inhibition of JNK with an inhibitor reduces embryopathy and yolk sac vasculopathy in high glucose-cultured mouse embryos,^{198,199} as does targeted disruption of the JNK2 enzyme where JNK2-KO diabetic mice have less malformed offspring than diabetic mice with intact JNK2.¹⁹⁸ Enhanced JNK activity has subsequently been demonstrated in rodent embryos exposed to diabetes in vitro and hyperglycemia in vivo and has been found to be associated with oxidative stress,²⁰⁶ apoptosis,^{200,206,207} and nitrosative stress.²⁰⁸

JNK activation thus appears to be one component in the teratogenic cascade of diabetic embryopathy.

Teratological processes provoked by diabetes

Several studies have suggested that diabetic embryopathy is associated with alterations of various signaling systems that result in disturbed intracellular conditions, such as oxidative stress,^{73,99,101,209} nitrosative stress,^{210,211} ER stress,^{195,211,212} and hexosamine stress.^{46,213} In addition, enhanced embryonic apoptosis^{88,89,104,123,200,207,214–216} has been regarded as a component of diabetic embryopathy (Table 41.5).

Oxidative stress

Oxidative stress reflects an imbalance between the production of ROS and an ability to detoxify the reactive intermediates or to repair the resulting damage. ROS can damage all components of the cell, including proteins, lipids, and DNA. Some ROS act as cellular messengers in redox signaling and a state of oxidative stress can therefore disturb



Figure 41.11 Hydroxyl radical.

normal cellular signaling. ROS are produced through multiple mechanisms, e.g., by NADPH oxidase (NOX) enzymes, and in mitochondria, where about 1%–2% of electrons passing through the electron transport chain are incompletely reduced and give rise to the superoxide radical ($\cdot O_2^-$). The ROS with the highest capacity to cause cellular damage is the hydroxyl radical (Figure 41.11), which, once formed, will alter DNA, RNA, proteins, lipids, or carbohydrates without being removed by any scavenging enzyme system.

The notion that diabetes is associated with oxidative stress has been suggested by several authors.^{217–221} For instance, increased lipid peroxidation and ROS generation were found in diabetic rats, measured as increased serum 8-epi-PGF_{2a} levels²²² and increased electron spin clearance rate.²²³ Cyclic voltammetric studies have also indicated increased levels of lipid peroxidation in diabetic rats,²²⁴ and the isoprostane 8-epi-PGF_{2a} is increased in embryos exposed to high glucose levels in vitro¹⁴⁷ and diabetes in vivo.¹⁵⁰ Examination of litters of diabetic rats demonstrated lowered a-tocopherol (vitamin E) concentration in day 11 embryos and in the liver of day 20 fetuses.⁸⁰

The first evidence of an involvement of oxidative stress in the pathogenesis of diabetic embryopathy was the demonstration that treatment of rodent embryos with antioxidative agents largely normalizes increased glucose-induced malformation rates in vitro,^{99,101} observations that were repeated^{102,132,225,226} and extended to in vivo studies.^{73,76,77,80,81,105,114,160,227–229} Furthermore, antioxidative treatment was found to normalize several markers of oxidative stress, such as serum 8-epi-PGF_{2a} levels,²²² electron spin clearance rate,²²³ and the concentration of embryonic isoprostanes in vitro¹⁴⁷ and in vivo.¹⁵⁰ Evidence for diabetes-induced oxidative stress has subsequently been found in several rat models of diabetic pregnancy.²³⁰

Several different compounds with antioxidative properties have been shown to diminish embryonic maldevelopment resulting from exposure to high glucose levels in vitro or to a diabetic intrauterine environment in vivo. Thus, adding scavenging enzymes, e.g., superoxide dismutase (SOD),⁹⁹ catalase,⁹⁹ or glutathione peroxidase,⁹⁹ to the culture medium protects rat embryos from dysmorphogenesis induced by high glucose concentration in vitro. The antioxidant NAC (Figure 41.12) blocks dysmorphogenesis in high glucose-cultured rodent embryos^{105,114,147,162,192,231} and neural crest cells (NCCs),^{232,233} and addition of glutathione ester to high-glucose medium diminishes embryonic maldevelopment.¹⁰²

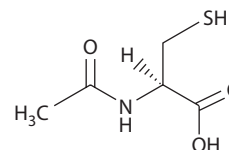


Figure 41.12 N-Acetylcysteine.

Table 41.5 Teratogenic processes

Oxidative stress—Confirmed teratogen in experimental studies
Hypoxic stress—Condition suggested to precede oxidative stress
Isoprostane formation—Confirmed teratogen in experimental studies
AGE/RAGE activity—Suspected teratogen in experimental studies
Nitrosamine stress—Suspected teratogenic process in experimental studies
ER stress—Suspected teratogenic process in experimental studies
Hexosamine stress—Suspected teratogenic process in experimental studies
Apoptosis—Enhanced embryonic process both before and after implantation

Actually, teratogenic concentrations of beta-hydroxybutyrate or the branched-chain amino acid analog KIC can also be blocked by the addition of SOD to the culture medium.¹⁰¹

Analogously, dietary supplementations with antioxidative compounds have been shown to diminish diabetic embryopathy *in vivo*. Thus, administration of BHT,⁷³ vitamin E,^{77,80,229} vitamin C,^{81,229} and folic acid,¹⁴⁹ diminishes the malformation rate in offspring of diabetic rats and largely improves embryonic and fetal growth *in vivo*. Alpha-lipoic acid supplementation has been found to diminish the high diabetes-induced incidence of resorptions and malformations in offspring of diabetic rodents.^{234–236} Embryos exposed to a diabetic intrauterine milieu have demonstrated diminished malformation rates after maternal supplementation of NAC.²³⁷ Combined supplementation of antioxidative compounds, e.g., vitamin E and C²²⁸ or folic acid and vitamin E,²¹⁶ to pregnant diabetic rats also diminished diabetes-induced dysmorphogenesis. In a study of glucose-induced cardiac malformations in a mouse model, the administered antioxidants diminished all negative effects of hyperglycemia/oxidative stress, such as hampered migration and increased apoptosis of NCCs, and prevented outflow tract defects.²³⁸

In addition, pregnant diabetic mice, transgenic for the CuZnSOD gene (SOD1), have fewer malformed offspring than their diabetic wild-type mice,^{209,210,212,239} illustrating the antiteratogenic capacity of increased ROS scavenging activity.

Embryonic neural tissue subjected to high glucose concentration shows increased superoxide production, as measured in a Cartesian diver system.²⁴⁰ One effect of increased intracellular ROS production would be inhibition of the rate-limiting enzyme of glycolysis, GAPDH, since this enzyme has displayed sensitivity to ROS in several different conditions of oxidative stress.²⁴¹ This sensitivity resides in the thiol group of cysteine residue 149 in the active site of the enzyme.^{242,243} Oxidation of the thiol group by NO or ROS leads to decreased enzyme activity,²⁴⁴ and blocking of this process by antioxidants protects the activity of the enzyme.²⁴⁵ Another mechanism for GAPDH inhibition also results from mitochondrial production of ROS, activating poly {ADP-ribose} polymerase 1 (PARP 1) by damaging DNA. PARP 1, in turn, induces ADP ribosylation of GAPDH, leading to its inactivation and an accumulation of metabolites earlier in the metabolism pathway. In line with these considerations, decreased GAPDH activity was found in rat embryos subjected to a diabetic environment both *in vivo* and *in vitro*,²⁴⁶ and furthermore, addition of the antioxidant NAC prevented the decrease in activity.²⁴⁶

In addition, fetuses and embryos of diabetic rodents display increased rates of DNA damage,^{71,86,247} another indication of enhanced ROS activity and damage in the embryonic tissues. High-amplitude mitochondrial swelling was demonstrated in the embryonic neuroectoderm of embryos exposed to a diabetic environment,^{248,249} a swelling diminished by antioxidative treatment of the mother,⁸⁵ implicating an embryonic ROS imbalance, with conceivable consequences for the rate of apoptosis in susceptible cell lineages in the embryo.^{231,250} The mitochondrion has an important role in

the apoptotic machinery, and previous studies have suggested that an altered apoptotic rate may affect the maldevelopment of embryos subjected to a diabetic milieu.^{104,214}

Furthermore, diabetic transgenic mice overexpressing thioredoxin-1 have a lower incidence of malformations and decreased oxidative stress markers than diabetic wild-type mice,²⁵¹ demonstrating a parallel relationship between dysmorphogenesis and degree of oxidative stress. Also, it has been suggested that diabetes-induced oxidative stress in embryos may cause maldevelopment via altered TNF-alpha levels.²⁵²

In a recent study of the activity of AMP-activated kinase (AMPK) in embryos of hyperglycemic mice, it was demonstrated that maternal hyperglycemia stimulated AMPK activity and that stimulation of AMPK with 5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside (AICAR) increased the rate of NTD in the embryos.²⁵³ In addition, stimulation of AMPK by hyperglycemia, hypoxia, or antimycin A could be inhibited by antioxidants. The AMPK inhibitor compound C blocked the effects of hyperglycemia or antimycin A on NTD occurrence, suggesting that diabetes-/glucose-induced stimulation of embryonic AMPK activity is a teratogenic consequence of oxidative stress in diabetic embryopathy.²⁵³ In support of that notion, it was reported in a subsequent study that sole stimulation of AMPK disrupts embryonic gene expression and causes NTDs.²⁵⁴

The bulk of data implicates oxidative stress and ROS excess as an important component in the etiology of diabetic embryopathy. The data also suggest that long-term exposure to high glucose creates embryonic ROS excess either from increased ROS production²⁴⁰ or from diminished antioxidant defense capacity.^{102,225,255} ROS excess may be small, restricted to particular cell populations,^{256,257} and likely vary with gestational time and nutritional status, making direct ROS determinations difficult.

Increasing ROS levels in embryos leads to malformations,^{258,259} suggesting that ROS excess may also have a role in the teratogenic process(es) of phenytoin medication,^{260,261} ethanol abuse,^{256,257,262} and, possibly, thalidomide administration.²⁶³ Therefore, ROS excess may constitute a common element in a number of teratogenic situations, including diabetic pregnancy.²⁶⁴

Hypoxic stress

In early organogenesis, oxygen levels are likely to be very low in the embryonic environment, and excess glucose metabolism could accelerate the rate of O₂ consumption, thereby exacerbating the hypoxic state. Since hypoxia can increase mitochondrial superoxide production, excessive hypoxia may contribute to oxidative stress. In a study of O₂ availability in embryos of glucose-injected hyperglycemic mice, it was found that O₂ availability was reduced by 30% in embryos of hyperglycemic mice.²⁶⁵ When pregnant hyperglycemic mice were housed in 12% O₂, the NTD rate increased eightfold in the offspring. Conversely, housing pregnant hyperglycemic mice in 30% O₂ significantly suppressed the effect of maternal diabetes to increase NTD.²⁶⁵ These observations suggest that maternal hyperglycemia depletes O₂ in the embryo

and that this contributes to oxidative stress and the adverse effects of maternal hyperglycemia on embryo development.

Isoprostane formation

Isoprostanes, e.g., 8-epi-PGF_{2α} (Figure 41.13), are prostaglandin-like compounds formed in situ from peroxidation of arachidonic acid by nonenzymatic, free radical-catalyzed reactions and therefore serve as indicators of lipid peroxidation.^{266–268} These nonclassical eicosanoids possess potent biological activity as inflammatory mediators. Also, the formation of isoprostanes may, in itself, consume arachidonic acid and therefore diminish the available pool of arachidonic acid in the embryo (see earlier). It has been shown that a diabetes-like environment increases isoprostane levels¹⁴⁷ in embryonic tissues. In addition, supplementation of 8-epi-PGF_{2α} to the culture medium caused malformations in the whole embryo culture, thereby illustrating the *independent teratogenic activity* of isoprostanes.²⁶⁹ Furthermore, adding SOD or NAC to the culture medium with isoprostane excess normalized almost all morphological and biochemical parameters, including the elevated tissue concentration of 8-epi-PGF_{2α}, thereby illustrating the teratogenic potential of diabetes-/glucose-induced oxidative stress.²⁶⁹

AGE formation and RAGE activation

The biochemical process of AGE formation, which is accelerated in diabetes as a result of chronic hyperglycemia and increased oxidative stress, has been postulated to play a central role in the development of diabetic complications.²⁷⁰ AGEs are known to accelerate oxidative damage to cells in a diabetic environment. Examples of AGE-modified sites are carboxymethyllysine (CML), carboxyethyllysine (CEL), and argpyrimidine. Under oxidative stress due to hyperglycemia in patients with diabetes, AGE formation is increased beyond normal levels.

RAGE, the receptor for AGE, is a transmembrane pattern recognition receptor. Except for AGEs, RAGE also has other agonistic ligands: the high-mobility group protein B1 (HMGB1), S100/calgranulins, amyloid-beta, and MAC-1. The interaction between RAGE and its ligands is thought to result in pro-inflammatory gene activation. Ligand stimulation of RAGE initiates a signaling cascade resulting in activation of NFκB and activation of NADPH oxidase, thereby yielding increased intracellular oxidative stress.

An increased accumulation of AGE has been found in the pathogenesis of several diabetic complications, such as cataract, retinopathy, atherosclerosis, neuropathy, and nephropathy. Inhibition or knockout of RAGE attenuates

the detrimental effects of hyperglycemia in neuropathy and nephropathy.²⁷¹

It has also been suggested that AGE–RAGE activation is involved in diabetic embryopathy. Thus, the embryonic formation of glycated proteins^{96,272,273} has been suggested to influence the teratological events in diabetic pregnancy. It has been shown in rodent embryos cultured in high glucose that the levels of the AGE precursor 3-Deoxyglucosone (3-DG) increase in embryonic tissue, and the addition of 3-DG to the culture medium with physiologic concentrations of glucose induces malformations, an effect that is reversible with the addition of SOD.⁹⁶

In a recent study of diabetic embryopathy with RAGE knockout mice, it was found that maternal diabetes induced more fetal resorptions, malformations (facial skeleton, neural tube), and weight retardation in the wild-type fetuses than in the RAGE^{−/−} fetuses, despite similar maternal hyperglycemia. In wild-type offspring, maternal diabetes increased fetal hepatic levels of 8-iso-PGF_{2α} and activated NFκB in the embryos, in contrast to unchanged 8-iso-PGF_{2α} levels and NFκB activity in diabetes-exposed RAGE^{−/−} offspring. These findings suggest that RAGE activation and oxidative stress are associated phenomenon in diabetic embryopathy (Ejdesjö et al., submitted).

Nitrosative stress

Nitrosamine overproduction, or *stress*, has been implicated in diabetic embryopathy, as a *downstream* event to oxidative stress. Thus, in a study of yolk sacs of CuZnSOD-(SOD1)-overexpressing embryos from normal and diabetic mice, it was found that the SOD1-transgenic embryos were largely protected from several of the negative effects of diabetes.²¹⁰ Thus, diabetes-induced elevated markers of oxidative stress (4-hydroxynonenal and malondialdehyde reductions) were diminished in the SOD1-transgenic embryos compared to the wild-type embryos. Furthermore, hyperglycemia-increased iNOS expression and nitrosylated protein were also diminished, and caspase-3 and caspase-8 cleavages were blocked, in the SOD1-transgenic embryos. This finding suggests that oxidative stress induces iNOS expression, nitrosative stress, and apoptosis in diabetic embryopathy.²¹⁰ In another study, diabetic pregnant mice were fed via gavage, an inhibitor of nitric oxide (Figure 41.14) (NO) synthase (NOS) 2, L-N6-(1-iminoethyl)-lysine (L-NIL; 80 mg/kg), once a day from embryonic (E) day 7.5–9.5 during early stages of neurulation. The treatment significantly reduced the NTD rate in the embryos, compared with that in the vehicle (normal saline)-treated diabetic group.²¹¹ In addition to alleviation of nitrosative stress, ER stress was also ameliorated, assessed by quantification of associated factors. Apoptosis was reduced, indicated by caspase 8 activation. These results show that nitrosative stress is

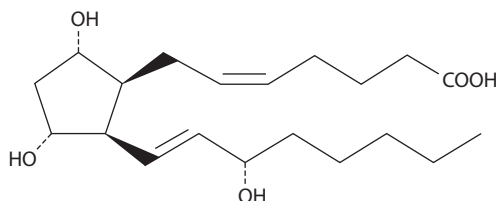


Figure 41.13 8-epi-PGF_{2α}.



Figure 41.14 Nitric oxide.

important in diabetes-induced NTDs via exacerbating ER stress, leading to increased apoptosis.²¹¹

The combined observations support a role for nitrosative stress in diabetic embryopathy, apparently as a consequence of oxidative stress.

ER stress

ER stress, also named unfolded protein response (UPR), is a cellular stress response related to the ER, which is induced by an accumulation of misfolded proteins in the ER lumen. The ER stress/UPR diminishes protein translation, degrades misfolded proteins, and produces chaperones involved in protein folding in order to restore normal ER function. If this is not achieved, or the disruption is prolonged, the ER stress/UPR shifts toward promoting apoptosis.

In a study of the effects of maternal diabetes on the development of oocytes and early embryos by using time-lapse live cell imaging confocal microscopy, the ER displayed an increased percentage of homogeneous distribution patterns throughout the entire ooplasm during oocyte maturation and early embryo development. In addition, a higher frequency of large ER aggregations was detected in oocytes and two cell embryos from diabetic mice. These results suggest that the diabetic condition adversely affects the ER distribution pattern during mouse oocyte maturation and early embryo development.²⁷⁴

In a study of oxidative and ER stress in SOD1-overexpressing mice, it was found that maternal diabetes causes increased levels of ER stress markers, e.g., C/EBP homologous protein (CHOP), calnexin, phosphorylated (p)-eIF2 α , p-PERK, and p-IRE1 α ; triggered XBP1 mRNA splicing; and enhanced ER chaperone gene expression in wild-type embryos, whereas all these changes were blocked in the embryos of diabetic transgenic mice. This supports the notion that diminishing diabetes-induced oxidative stress, e.g., by SOD1 overexpression, blocks ER stress in embryos.²¹²

A downstream effect of the ER stress would be an activation of JNK. The possible relationship between JNK1/2 activation and ER stress in diabetic embryopathy was investigated in mice. Maternal diabetes increased ER stress markers and induced swollen/enlarged ER lumens in embryonic neuroepithelial cells during neurulation. Deletion of both JNK1 or JNK2 genes diminished hyperglycemia-increased ER stress markers and ER chaperone gene expression. In high glucose-cultured embryos, the addition of the ER chaperone 4-phenylbutyric acid (4-PBA) diminished ER stress markers and abolished the activation of JNK1/2 and its downstream transcription factors, caspase 3 and caspase 8, as well as Sox1 neural progenitor apoptosis. Consequently, 4-PBA blocked high glucose-induced NTD in vivo. It was concluded, therefore, that hyperglycemia induces ER stress, which yields the activation of proapoptotic JNK1/2 pathway, which yields induced neural tube apoptosis and thereby NTD.²⁷⁵

Autophagy is an intracellular process to degrade dysfunctional proteins and damaged cellular organelles, which, in

addition, regulate embryonic cell proliferation, differentiation, and apoptosis. Furthermore, blockage of this process in embryos causes NTDs reminiscent of those observed in diabetic pregnancies. In a study of NTD induction in diabetic mice with or without 2%–5% trehalose water, the role of autophagy was investigated. Maternal diabetes suppressed autophagy in neuroepithelial cells and altered autophagy-related gene expression. Trehalose treatment reversed autophagy impairment and prevented NTDs in the embryos of diabetic pregnancies. The study demonstrates that maternal diabetes suppresses autophagy in neuroepithelial cells of the developing neural tube, leading to NTD formation.²⁷⁶

In a recent study of diabetes-induced cardiac malformations, it was found that the rate of atrioventricular septal defects (AVSDs) was increased concomitant with enhanced ER stress in embryonic hearts. Blocking of glucose-induced ER stress with 4-PBA in an endocardial cushion explant culture restored endocardial cell migration. The findings suggest that the development of endocardial cushions is susceptible to the insult of maternal hyperglycemia, and that diabetes-induced ER stress in the developing heart mediates the negative effect on endocardial cell migration.²⁷⁷

The studies suggest that ER stress, downstream of oxidative stress, is involved in the teratogenesis of neural and cardiac malformations in embryos exposed to diabetes or hyperglycemia.

Hexosamine stress

Increased ambient glucose concentration yields increased uptake, phosphorylation, and metabolism of glucose, primarily by enhanced flux in the glycolytic pathway and, also, in the hexosamine biosynthetic pathway.¹¹⁸ This is a pathway that converts glucose to uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc) (Figure 41.15).

Under normoglycemic conditions, approximately 1%–3% of total glucose consumed by somatic cells is directed down the hexosamine pathway.²⁷⁸ UDP-GlcNAc is the substrate for the majority of glycosylation in the cell, producing mucopolysaccharides.²⁷⁹ In this process, UDP-GlcNAc is attached to serine or threonine residues of proteins, thus becoming a posttranslational modification (beta-O-linked glycosylation), which regulates protein function in an analogous manner to phosphorylation.²⁸⁰ Altered beta-O-linked glycosylation has been associated with a number of disease states, including cancer, inflammatory conditions, and neurodegenerative diseases.²⁸¹ Notably, it is also implicated as a primary mechanism

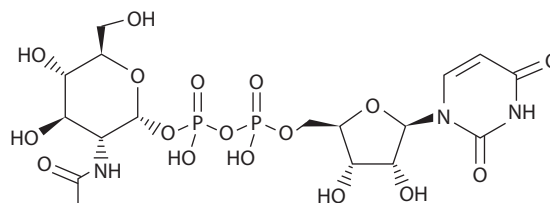


Figure 41.15 UDP-GlcNAc.

behind the development of insulin resistance and pancreatic beta-cell destruction in type 2 diabetes.^{278,281}

It has been suggested that hexosamine stress may have a role in diabetic teratogenesis.^{46,213,282} Indeed, defect development has been demonstrated in preimplantation mouse embryos, treated with glucose (27 mM) or glucosamine (0.2 mM) that was added to embryo culture media. Both treatments disturbed embryo development, increased apoptosis, and decreased cell number in the resulting blastocysts.²⁸² Addition of benzyl-2-acetamido-2-deoxy- α -D-galactopyranoside (BADGP), an inhibitor of O-linked beta-N-acetylglucosaminyltransferase (OGT), the enzyme that adds O-GlcNAc to proteins, rescued all these phenotypes in the hyperglycemia treatment group, although only mild improvement was seen in the glucosamine group.²⁸² This may reflect the relative potencies of each hexose in their capacity to stimulate UDP-GlcNAc production.²⁷⁸ In another study, pregnant mice were injected with glucose to induce hyperglycemia, or glucosamine, to directly activate the hexosamine pathway. Both treatments increased the NTD rate in the embryos, decreased GSH levels, and increased oxidative stress, as indicated by increased 2,7-dichlorodihydrofluorescein fluorescence. Glucose and glucosamine also inhibited expression of Pax-3; however, all these effects were prevented by GSH ethyl ester administration.²¹³

These findings suggest a role for hexosamine stress in diabetic embryopathy.

Apoptosis

The notion that apoptosis may be a component of the teratogenic process of diabetic pregnancy has been studied thoroughly. Thus, there are several reports of an increased rate of apoptosis in embryos exposed to a diabetic environment.^{88,89,200,206,207,215,216,231,250,283,284} In particular, there are findings indicating increased apoptotic rate already in preimplantation embryos.^{104,123,214}

In a study of early postimplantation embryos, the expression of Bcl-2 mRNA was decreased, and the number of deoxynucleotidyl transferase-mediated nick end labeling (TUNEL)-positive cells increased in embryos of diabetic rats compared to control. These results suggest that a Bax-regulated mitochondrial cytochrome c-mediated caspase-3 activation pathway might be involved in diabetic embryopathy.²¹⁵ In another early study, it was reported that combined supplementation of folic acid and vitamin E to pregnant diabetic rats diminished diabetes-induced dysmorphogenesis and normalized apoptotic-associated protein levels.²¹⁶ In another study of rodent embryos subjected to high glucose in vitro or diabetes in vivo, disturbed development was found, concomitant with increased activation of caspase 3 and other markers of apoptosis. Supplementation of NAC or an apoptosis inhibitor diminished both dysmorphogenesis and apoptosis.²³¹ Exposure to a diabetic milieu during organogenesis thus increases dysmorphogenesis and apoptosis in embryos.

In mice, transgenic for the thioredoxin-1 gene with overproduction of the antioxidant thioredoxin-1, the incidence

of diabetes-induced malformation is markedly lower in diabetic transgenic mice compared with diabetic wild-type mice. Furthermore, the diabetes-induced increased markers for oxidative stress, apoptosis-promoting proteins, and cleaved caspase-3 production are all diminished in the offspring of diabetic transgenic mice compared with the offspring of diabetic wild-type mice.²⁵¹

A new apoptotic pathway was recently suggested to be activated by a diabetic/hyperglycemic environment, involving the ASK1-FoxO3a-TRADD-caspase 8 gene products.²⁰⁷ Blocking components of this pathway diminished the NTD rate in diabetic mice. Thus, hyperglycemia-induced apoptosis and the development of NTDs were reduced with genetic blockage of either FoxO3a or Casp8, or by inhibition of ASK1 by thioredoxin. In addition, examination of human neural tissues affected by NTDs revealed increased activation or abundance of the genes in the cascade. The conclusion was that activation of the ASK1-FoxO3a-TRADD-caspase 8 pathway participates in the development of NTDs, which could be prevented by inhibiting intermediates in this cascade.²⁰⁷

There is, evidently, strong experimental evidence for the role of apoptosis in diabetic embryopathy (Figure 41.16).

Genetics and epigenetics of diabetic dysmorphogenesis (Table 41.6)

Genetic predisposition

Despite similar teratological exposure, the effect of any teratogen, including maternal diabetes/hyperglycemia, varies between individuals. In addition to stochastic conditions, genetic predisposition determines the effect of each teratogen on a particular individual.^{285,286} Although predisposing genetic conditions for diabetes are clearly present in offspring of diabetic parents,^{287,288} as the offspring of a diabetic father has a higher risk of developing the disease than the offspring of a diabetic mother,^{289–293} it has been established that diabetic men do not have an increased risk of fathering malformed offspring.^{294,295} This indicates that the genes predisposing to diabetes do not induce congenital malformations. In contrast, maternal diabetes has been suggested to be associated with Down's syndrome^{296–298} and has also been suggested to predispose for optic nerve hypoplasia in female offspring.²⁹⁹ A genetic element may be present in the etiology of diabetic embryopathy,³⁰⁰ a notion supported by experimental data.^{69,95,209,301–304}

The contribution of the fetal genome and maternal (diabetic) environment was evaluated in a rat model where the outcome of diabetic pregnancy in two outbred substrains of Sprague Dawley rats (with low incidence {H} and high incidence {U} of skeletal malformations in the offspring) and in F1 hybrids between them.⁹⁵ The fetuses of diabetic H mothers had no skeletal malformations, regardless of embryo type (H/H or H/U). When the diabetic mother was U or from the hybrid strain (H/U) and the offspring of the mixed H/U type, increased skeletal malformation (3%–5%) rates resulted. When the embryos contained a

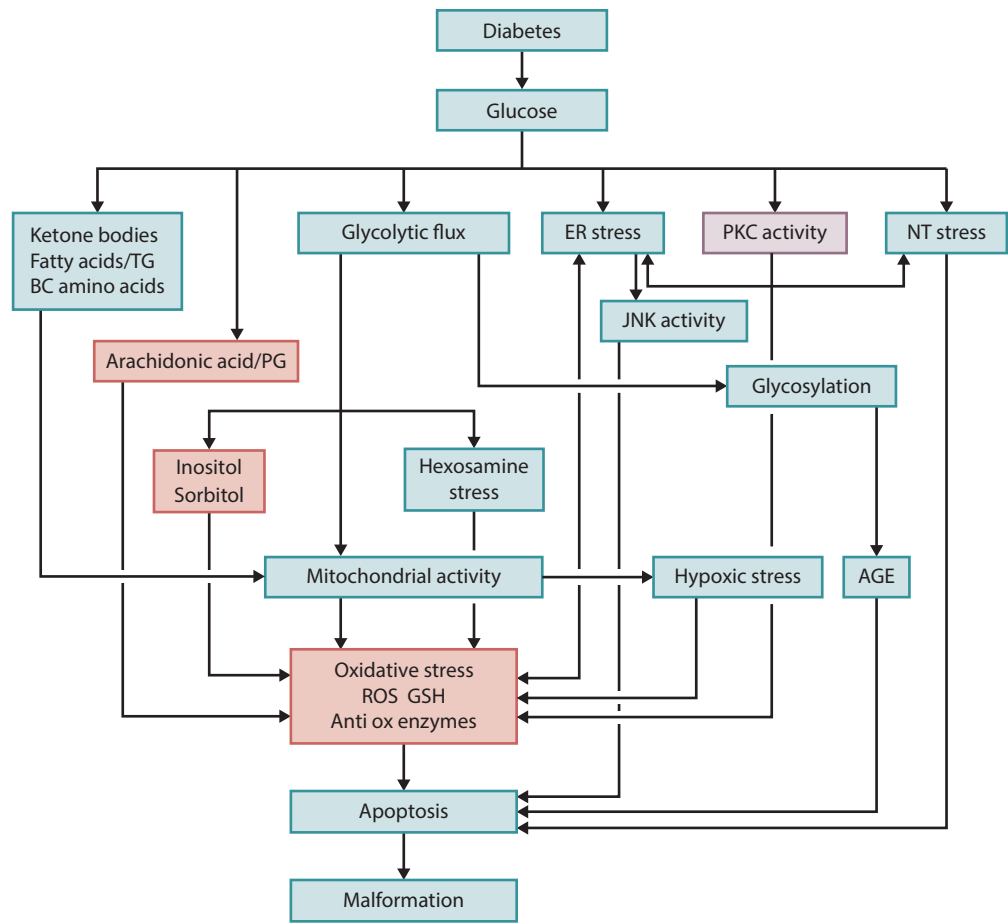


Figure 41.16 Schematic outline of the development of diabetic embryopathy. Blue color marks increased activity/amount and red color decreased activity/amount of compounds or processes (mixed blue–red color marks mixed effect—both increased and decreased). Note that more interactions between the items are likely to be present than those denoted here and that the epigenetic/genetic alterations are not included.

Table 41.6 Conditions of teratogenesis
Genetic predisposition—Individual teratological susceptibility
Gene expression—Part of the teratogenic process
Epigenetics—Part of the teratogenic process

major U genome (either U/U or U/(H/U)), further increased skeletal malformations (17%–19%) were found. These findings indicate that both the maternal and fetal genome are involved in the etiology of diabetes-induced (skeletal) malformations in rodent diabetic pregnancy.⁹⁵ Also, when pre-implantation embryos were transferred from diabetic NOD mice to nondiabetic Institute for Cancer Research (ICR) mice and allowed to develop until gestation day 13, as was embryos from the reverse transfer, as well as from an ICR-to-ICR transfer, there were 8/58 (14%), 18/45 (40%), and 0/73 (0%) malformed embryos in the NOD–ICR, ICR–NOD, and ICR–ICR transfers, respectively. The result thus suggests that both the embryo genotype and the maternal environment are of importance for diabetic embryopathy.⁶⁹ Also, in a recent study, one-cell mouse zygotes and blastocysts were transferred from diabetic or control mice to nondiabetic

pseudopregnant female recipients and were evaluated at embryonic day 14.³⁰⁵ The offspring from diabetic rats had higher rates of malformations than the controls, and the conclusion was that exposure to maternal diabetes during oogenesis, fertilization, and the first 24 hours is enough to program permanently the fetus to develop significant morphological changes.³⁰⁵ In order to characterize the relative importance of the maternal and paternal genome in relation to the teratogenicity of the maternal (intrauterine) milieu, rats from two different strains were cross mated. Thus, male rats from a malformation-prone (L) and a malformation-resistant (W) strain were mated with diabetic females from the other strain to produce F1 offspring—LW (L male × W female) and WL (W male × L female)—which would be genetically identical with exception for imprinted genes and mitochondrial types. However, the malformation rate was 0% in the LW and 9% in the WL offspring,¹³⁸ demonstrating both a teratologic *dilution* effect and the importance of the maternal environment. Based on metabolic data from the two types of pregnancy (indicating a more disturbed metabolic state in the diabetic L rats), the study suggested that the fetal genome controls the embryonic dysmorphogenesis in diabetic pregnancy by instigating a threshold level for the teratological insult and that the maternal genome controls

the teratogenic insult by (dys)regulating maternal metabolism.¹³⁸ Furthermore, when the F1 crosses were mated in a subsequent study, the malformation rates of the F2 combinations, WL $\times$ WL_{diabetic} and LW $\times$ LW_{diabetic}, were around 5%,³⁰⁶ a further dilution of the teratogenic induction; however, the malformed WL $\times$ WL offspring only had agnathia/micrognathia, whereas the malformed LW $\times$ LW offspring had 60% agnathia/micrognathia and 40% cleft lip and palate. Thus, despite identical autosomal genotypes, the diabetic WL and LW female rats gave birth to offspring with markedly different malformation patterns. This study suggested a teratological mechanism in diabetic pregnancy influenced by maternal metabolism and parental strain epigenetics.³⁰⁶

In a previous study, it could be demonstrated that a specific variant of the catalase enzyme is present in rats that are malformation-prone (*Cs-1a*), whereas another variant of the catalase protein was present in rats that do not develop malformations in response to maternal diabetes (*Cs-1b*).³⁰³ Thus, embryonic catalase activity was lower in embryos from normal U rats than in embryos from normal H rats, and maternal diabetes augments this difference.³⁰⁴ The catalase cDNA and the promotor region of the catalase gene in the U and H rat were sequenced³⁰⁷ and yielded one nucleotide mutation in the 5'-UTR-region of the U rat cDNA and a heterozygosity in the U rat gene promoter. Therefore, the decreased catalase mRNA levels may result from a different regulation of transcription (promotor), and the difference in the electrophoretic mobility in zymograms³⁰³ may be a result of posttranslational modifications of the catalase protein.

Using an inbred Sprague Dawley strain (L) with about 20% skeletal malformations when the mother is diabetic and inbred Wistar Furth rats (no diabetes-inducible skeletal malformations), a global gene linkage analysis of the skeletal malformations was performed with microsatellites, a study that yielded strong coupling of the malformations to 7 regions on chromosomes 4, 10, 14, 18, and 19 and a weaker coupling to 14 other loci in the genome; altogether we found loci on 16 chromosomes. Searching for candidate genes within a distance of 10 cM from each microsatellite yielded 18 genes that had been implicated in previous studies of diabetic embryopathy. These genes were involved in embryonic development/morphogenesis (*Map1b*, *Shh*, *Tgfb3*, *Vegfa*, *Dvl2*, *Nf1*, *Gsk3b*, *Gap43*, *Tgfb3*, *Gdf1*, *Csf1r*),^{308–314} regulation of DNA/RNA metabolism (*En2*, *Brcc3*, *Tp53*),^{192,308,315–317} regulation of apoptosis (*Nol3*, *Bak1*),³⁰⁸ and cellular metabolism (*Folr1*, *Akr1b1*).^{149,168,315}

Gene expression

Altered gene expression in the offspring has been found in several studies^{308,311,313–315,318–322} and appears to be an integral component of diabetic embryopathy.³²³

The Pax-3 gene expression has been found to be reduced in embryos of diabetic mice,^{88,89} and this transcription factor may regulate the gene expression of the licensing factor *cdc-46*³²⁴ and a gene, *Dep-1*,³²⁵ as well as p53,³¹⁶ all of which may be of importance for a correct neural tube closure. Null mutation of the Pax-3 gene yields the *Spotch* mouse displaying NTDs.^{88,326} It has also been shown that the decreased

Pax-3 expression in embryos of diabetic mice could be normalized by treatment of the mother with antioxidants,²⁶⁵ thereby demonstrating a coupling between ROS excess and a teratologically important change in gene expression. In a later study, NCCs of Pax3-deficient embryos displayed impaired migration and increased apoptosis. Suppression of p53, by either null mutation of the p53 gene or administration of a p53 inhibitor, pifithrin- α , prevented the defective NCC migration and apoptosis in Pax3-deficient embryos and also restored proper development of cardiac outflow tracts. Pax3 thus appears to be required for cardiac outflow tract septation because it blocks p53 expression during NCC migration.³¹⁷

The embryonic expression of genes controlling the defense against oxidative stress is sensitive to maternal diabetes. Thus, in a study of pregnant diabetic rats, the embryos demonstrated decreased expression of CuZnSOD and MnSOD.³²⁷ In addition, the expression of Gpx-1 and Gpx-2 was decreased compared with embryos from normal rats, enzymes that function in the detoxification of hydrogen peroxide, an important antioxidant system. The decrease in gene expression of Gpx-1 was further enhanced in the malformed embryos. The immunostaining of Gpx-1 displayed a general accumulation of positive cells in the cardiac tissue of all embryos. However, the nonmalformed embryos had less staining than embryos from normal rats and malformed embryos from diabetic rats had almost no staining at all.³²⁷

In a study of cardiac malformations in diabetic mouse pregnancy demonstrating dilated heart tube, smaller ventricles, conotruncal stenosis, and abnormal heart looping, ventricular septal defects were observed and actors in the TGF- β signaling that regulate heart development were downregulated by maternal diabetes. It was concluded that TGF- β signaling is involved in cardiac malformations in diabetic embryopathy.³¹¹ Also, in a study of global gene expression in a transgenic mouse model of caudal dysgenesis and in a pharmacological model using in situ hybridization and quantitative real-time PCR, altered expression of several molecules that control developmental processes and embryonic growth was noted. The most pronounced finding was that of altered Wnt signaling, which suggests that impaired signaling in this pathway may be involved in diabetic embryopathy.³¹³ A genome-wide investigation of gene expression in embryos from normal and diabetic mice followed by quantitative RT-PCR yielded several genes with altered expression. Sequence motifs in the promoters of diabetes-affected genes suggest potential binding of transcription factors that are involved in responses to oxidative stress and/or to hypoxia, and furthermore, around 30% of the diabetes-affected genes encoded transcription factors and chromatin-modifying proteins or components of signaling pathways that affect transcription.³¹⁸ In a genome-wide expression profiling in the developing heart of embryos from diabetic and control mice, it was found that a total of 878 genes exhibited more than 1.5-fold changes in the expression level in hearts of experimental embryos compared with their respective controls. Several genes involved in a number of molecular signaling pathways such as apoptosis, proliferation, migration,

and differentiation in the developing heart were differentially expressed in embryos of diabetic pregnancy.³²²

Several different genes and pathways have been demonstrated to be affected in diabetic pregnancy; however, there is not, as yet, any universal gene identified to be responsible for enhanced (or decreased) susceptibility to diabetic embryopathy.

Epigenetics

There are considerable indications that epigenetic processes have a role in diabetic embryopathy.^{319,328–334}

In a seminal study, it was found that transient hyperglycemia induced long-lasting activating epigenetic changes in the promoter of the NFκB subunit p65 in aortic endothelial cells both in vitro and in nondiabetic mice, resulting in increased p65 gene expression. Both the epigenetic changes and the gene expression changes persisted for at least 6 days of subsequent normal glycemia. Furthermore, the hyperglycemia-induced epigenetic changes and increased p65 expression were prevented by reducing mitochondrial superoxide production or superoxide-induced alpha-oxaldehydes.³²⁸

Analysis of gene expression data from two sets of embryos of diabetic mice suggested that maternal diabetes may increase the overall variability of gene expression levels in embryos. The suggestion was that altered gene expression and increased variability of gene expression together constitute the molecular correlates for the incomplete phenotype penetrance in diabetic pregnancy. Based on this model, it was suggested that maternal diabetes reduces the precision of gene regulation in exposed individuals. Loss of precision in embryonic gene regulation may include changes to the epigenome via deregulated expression of chromatin-modifying factors.^{319,329}

In a study of maternal diabetes effect on DNA methylation of imprinted genes in oocytes, it was found in SZ-induced diabetic and NOD mice that the methylation pattern of Peg3 differential methylation regions (DMR) was altered, and in the SZ-induced mice, demethylation was observed on day 35 after SZ injection. The expression level of DNA methyltransferases (DNMTs) was also decreased in diabetic oocytes. These results indicate that maternal diabetes has adverse effects on the DNA methylation of maternally imprinted gene Peg3 in oocytes, but also that methylation in the oocytes of the offspring is normal.³³¹ Also, the expression was increased and the methylation level of H19 was decreased, whereas the expression and methylation levels of Peg3 was completely opposite in placentas of diabetic mice. When embryos of normal females were transferred to normal/diabetic pseudopregnant females, the methylation and expression of Peg3 in placentas were also clearly altered in the normal-to-diabetic group compared to the normal-to-normal group. However, when the embryos of diabetic female were transferred to normal pseudopregnant female mice, the methylation and expression of Peg3 and H19 in placentas were similar between the two groups. The data suggest that the effects of maternal diabetes on imprinted genes may primarily be caused by the adverse uterus environment.³³²

In a study, NSCs were exposed to high glucose/hyperglycemia and alterations were found in chromatin reorganization, global histone H3 status, and global DNA methylation,

as well as increased expression of Dcx and Pafah1b1 and decreased expression of four microRNAs targeting these genes. This study suggested that hyperglycemia alters the epigenetic mechanisms in NSCs, resulting in the altered expression of developmental genes.³³³ In a genome-wide survey of histone acetylation in neurulation stage embryos from diabetic mouse pregnancies, it was found that exposure to maternal diabetes and, independently, exposure to a high-fat diet were associated with increases and decreases of H3 and H4 histone acetylation, respectively, in the embryo. These data suggest that epigenetic changes in response to the diet and metabolic condition may contribute to the increased risk for NTD in diabetic and obese pregnancies.³³⁰

In a study of embryos of pregnant hyperglycemic mice and mouse ESCs, the methylation of a Pax3 CpG island was decreased in embryos and ESCs. Use of shRNA in ESCs demonstrated that DNA methyltransferase 3b (Dnmt3b) was responsible for the methylation and silencing of Pax3 prior to differentiation and by oxidative stress. These results indicate that hyperglycemia-induced oxidative stress stimulates Dnmt3b activity, thereby inhibiting chromatin modifications necessary for induction of Pax3 expression and, thus, providing a molecular mechanism for defects caused by Pax3 insufficiency in diabetic pregnancy.³³⁴

Epigenetic changes in the embryo caused by maternal diabetes are likely to be transferring the teratogenic input of the diabetic environment. Identifying these changes is important both for the increased knowledge generated and also for the possible antiteratological treatment that may emerge from the identified mechanisms.

Conclusions and future directions

From the previous discussion, it is evident that diabetic embryopathy has a complex etiology and pathogenesis. The studies of etiologic factors in the pathogenesis of congenital malformations have revealed a scenario in which the diabetic state simultaneously induces alterations in a series of teratogenically capable pathways. These pathways are intertwined, and several of them result in an imbalance of the ROS metabolism, yielding ROS excess in teratogenically sensitive cell populations, an imbalance ultimately causing congenital malformations. Blocking the ROS excess may be one valid way to diminish the disturbed development caused by the diabetic environment (Table 41.7).

Downstream of the oxidative stress, however, several conditions of cellular stress are present, such as nitrosative, ER, hypoxic, and hexosamine stress, as well as a possible teratogenic involvement of AGEs. In this area of metabolites and

Table 41.7 Conclusions and future directions
What is the current <i>level of understanding</i> of the teratogenic process of diabetic embryopathy?
Are there any putative <i>target molecules/pathways</i> that we could possibly utilize to prevent malformations?

pathways, there may be possibilities of finding a molecule to use for intervention therapy.

There is also a growing understanding of the diabetes-induced alterations in genetic and epigenetic systems, which will, again, increase our knowledge and, hopefully, inspire to develop new ways to block diabetic embryopathy in the future.

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42 Fetal malformations detected with magnetic resonance imaging in the diabetic mother

Tuangsit Wataganara

Introduction

Diabetes mellitus is one of the most common medical disorders during pregnancy, affecting approximately 3%–10% of women. Gestational diabetes mellitus accounts for 80%–90% of cases of diabetes mellitus in pregnancy, while preexisting type 2 diabetes accounts for approximately 10%–20%.¹ Abnormal glucose metabolism results in persistent or postprandial elevation of blood sugar level. Elevation of blood sugar level during pregnancy is linked to suboptimal perinatal outcomes, including miscarriage, fetal malformations, stillbirth, and birth asphyxia. Diabetes mellitus is considered a major risk factor for abnormal fetal development. More women are expected to have diabetes mellitus during pregnancy due to older age at the time of conception, a growing rate of obesity, and the change in diagnostic criteria for gestational diabetes.

Congenital anomalies are more commonly found in babies born from diabetic mothers. This risk has been thought to be higher in pregnancy complicated with type 1 (insulin dependent) diabetes mellitus.² Recently, type 2 (non-insulin-dependent) diabetes mellitus was proven to be equally embryopathic.³ The chance of fetal malformation in pregnant women with diabetes mellitus is as high as 13.3%, compared to 1%–2% in low-risk groups.⁴ The pathogenesis of fetal malformations in diabetic mothers is multifactorial. Poor glycemic control in peri- and early conceptional period is a strong determination factor for fetal anomaly. Optimal blood sugar control can be monitored by the level of hemoglobin A_{1C} (Hb A_{1C}). Two-thirds of diabetes-related birth defects involve the cardiovascular system and central nervous system (CNS).¹ The risk of fetal malformation is not increased when HbA_{1C} at 14 weeks is less than 7%. The chance of fetal malformation can be as high as 22% if Hb A_{1C} level is higher than 8.5%.⁵

Due to the higher chance of fetal malformations, detailed routine fetal ultrasound examination is offered in pregnant women with diabetes mellitus, especially for those with poor glycemic control in the first trimester.

Prenatal detection of anomaly can lead to a more targeted counseling, timely intervention, fetal therapy, and appropriate neonatal management. Most of the fetal anomalies are detected by ultrasound in the second trimester. Recently, magnetic resonance imaging (MRI) has been used as an adjunct when limitations of fetal ultrasound are encountered. This chapter is focused on the additional benefit of MRI in the detection of fetal malformations related to diabetes mellitus.

Comparison of fetal ultrasound and magnetic resonance imaging

Ultrasound and MRI are considered as complementing imaging technologies. Ultrasound has been the principal imaging modality in fetal medicine. In theory, ultrasound beam may cause thermal and nonthermal changes at the subcellular level. This phenomenon has never been proven to be of clinical significance.⁶ Ultrasound is safe, convenient, affordable, and widely available in most places. Real-time interpretation of fetal anatomy can be accomplished by the perinatologist. Fetal well-being can also be readily assessed by the observation of fetal movement pattern and Doppler interrogation of fetal, placental, and uterine vessels. Off-line analysis is possible with a 3D computerized ultrasound system.⁷ Fetal ultrasound has some limitations. Most fetal anomalies or damages will be seen on the ultrasound only when they are at their later stages. View during examination may be obstructed by fetal position, reduced liquor volume, maternal adiposity, or bony structures. Assessment of fetal brain may not be adequate if the head is engaged deep down in the pelvic canal. Obesity and oligohydramnios always compromise the accuracy of ultrasound diagnosis.⁸ Ultrasound has a smaller field of view; therefore, the interpretation heavily relies on the experience of the operator.

With these limitations of the fetal ultrasound examination, MRI has been advocated in selected cases of fetal

anomaly suspected from the ultrasound. MRI has an advantage of excellent tissue contrast. This quality allows for the detection of subtle fetal malformation and early changes that may lead to fetal damage. The MRI field of view is relatively large. Surrounding maternal structures can be simultaneously evaluated to determine their relationship with the uterus and placenta, especially when surgical intervention is planned. Unlike fetal ultrasound, maternal adiposity and bony structure do not affect the quality of MRI image. MRI data can be interpreted off-line by specialists. For instance, neurogeneticists can help determine the significance of the subtle findings in the developing fetal brain at various gestational ages. MRI can also improve the understanding of the whole fetal care team, including nurses, genetic counselors, and social workers. Limitations of fetal MRI exist. Its high cost naturally limits broader availability. Strict indications for fetal MRI have been implemented in many places where both fetal ultrasound and fetal MRI are offered. MRI is very sensitive to fetal movement. Motion artifact, as shown in Figure 42.1, can occur, even with the ultrafast MRI protocol that takes only 20 seconds to complete the scan.

The comparison between ultrasound and MRI imaging in the fetus is summarized in Table 42.1.

Principles and techniques of fetal magnetic resonance imaging

MRI is an alternative imaging method that can confirm or complement abnormal ultrasound findings. Its use in pregnant women was first described in 1983.⁹ The original obstetric indication for MRI was to assess myometrial invasion of placenta accreta. Its application in fetal medicine was previously limited because the original MRI sequence protocol was subjected for a significant motion artifact. Maternal and fetal sedation were commonly practiced to reduce movement and to compensate for a long examination time. Fetal MRI has regained broader application after the development of ultrafast MRI sequences in the 1990s. The single-shot rapid acquisition with focused echoes is a high-quality T2-weighted sequence that acquires a slice in less than a second.¹⁰ The preferred system for fetal MRI consists of 1.5 T

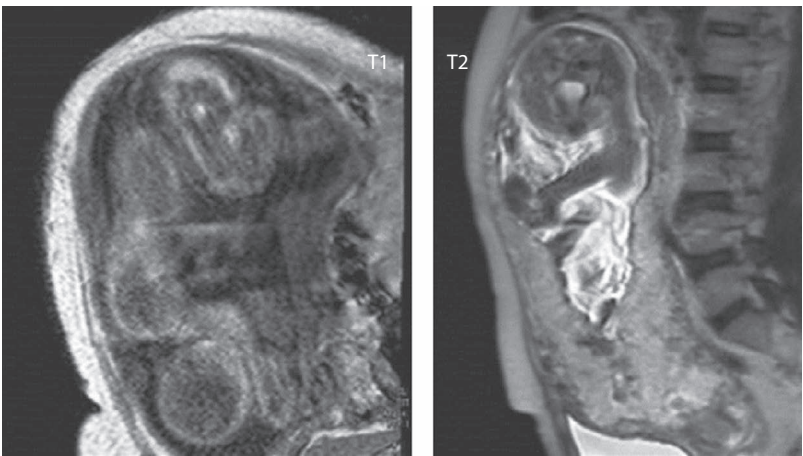


Figure 42.1 Magnetic resonance imaging (MRI) is extremely sensitive to fetal movement. The motion artifact can equally affect the image quality of both T1- and T2-weighted gradient. Development of ultrafast fetal MRI protocol as well as optimal patient preparation can reduce the artifact and improve the image quality.

Table 42.1 Comparison between ultrasound and magnetic resonance imaging for an assessment of fetal anatomy		
	Ultrasound	MRI
Advantages	Safe Convenient Inexpensive More experienced	Better soft tissue contrast, especially intracranial and intrathoracic lesion Large field of view Off-line interpretation
Disadvantages	Maternal obesity Oligohydramnios Operator dependent	Expensive Not widely available Subjected to motion artifact Less experienced Limitation in fetal cardiac assessment and intravenous contrast study

resonators with multichannel coils. MRI can measure volume of fetal organs in three dimensions. For instance, total lung volume in case of congenital diaphragmatic hernia can be used to predict neonatal survival.¹¹ Assessment of fetal intracranial and intrathoracic lesions has also been benefited from the superb soft tissue delineation of MRI.

Most literatures suggest the safety of MRI used in pregnancy.^{12,13} Many professional organizations discourage its use during the first trimester.¹⁴ By nature, spontaneous miscarriage occurs more frequently in the first trimester. It could be perceived as iatrogenic by the patients if the incidence occurs soon after the MRI session. The patient can be assured that there has been no known risk to the fetus if MRI is offered in the late second or third trimester.¹² Maternal claustrophobia, pacemaker, and ferromagnetic implants remain the contraindications of MRI during pregnancy.¹⁵

Good preparation can help improve the image quality from MRI sequence. The mother is advised not to eat or drink at least 4 hours prior to the examination. This is to reduce motion artifacts from bowel movement and to prevent excessive fetal activity after meal. Written informed consent should be obtained. Fetal sedation is not mandatory. Screening ultrasound examination should be performed immediately before the MRI examination to confirm fetal viability. The mother is usually in supine position. First shots can be done to adjust for the signal density, as shown in Figure 42.2. Single-shot rapid acquisition T2-weighted images with refocused echoes in the axial, coronal, and sagittal planes are obtained. T1-weighted images are also acquired, since it can better depict fat and hemorrhage.¹⁶ Intravenous contrast study with gadolinium is discouraged, because it rapidly crosses the placenta and its fetal safety profile has not been clearly shown.¹⁷

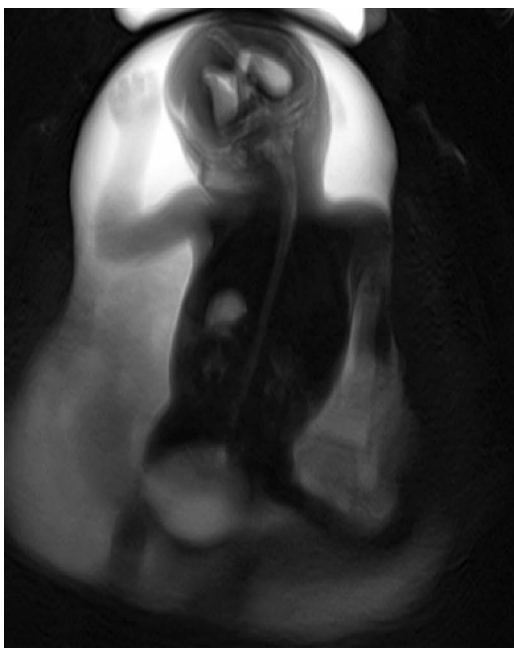


Figure 42.2 First magnetic resonance imaging shots can help in the formation of an overall position of the fetus. Note the spina bifida with protruded meningeal sac at the sacral end of this baby.

Fetal anomalies related to maternal diabetes

Poor glycemic control in periconceptional period and early gestation has been linked to malformation in various fetal organ systems, especially the cardiovascular system and CNS. Anomalies in fetal gastrointestinal, renal, and skeletal systems are also linked to maternal diabetes mellitus. Fetal cardiac defects commonly associated with maternal gestational diabetes include ventricular septal defect and conotruncal anomalies (such as transposition of the great arteries and truncus arteriosus). Cardiomyopathy that leads to intrauterine congestive heart failure has also been observed in diabetic mothers with poor glycemic control.¹⁸

The overall prevalence of neural tube defect (NTD) is 2–5 per 1000 live births. Maternal diabetes mellitus is associated with a 16-fold increase incidence of fetal NTD. Anencephaly and spina bifida are the two most common NTD related to maternal diabetes mellitus.¹⁹ There is also a significant increase in the incidence of encephalocele in infants born from diabetic mothers.²⁰ The incidence of fetal spina bifida is even higher when the pregnancy is complicated with obesity.²¹ Obesity and diabetes mellitus is strongly interrelated.

Neural tube is a primitive bundle of nerves that folds to form brain at the front end and spinal cord at the rear end. Failure of this structure to close on the 28th conception day results in a broad spectrum of NTDs. Anencephaly and spina bifida are the most common variants of NTD. The former begins with maldevelopment of the skull (acrania) with protrusion of the brain (exencephaly). The brain is then destroyed by its exposure to amniotic fluid.

Fetal caudal regression, or sacral agenesis, syndrome is an anomaly that strongly related to maternal diabetes mellitus. The risk of caudal dysplasia increases remarkably, up to 600 times higher in infants born from diabetic mothers.¹⁹ This malformation consists of agenesis of the lumbar vertebrae, sacrum, and coccyx. Fetal lower extremities are poorly developed. Renal malformations, such as hydronephrosis, ureteral duplication, and renal agenesis, are also commonly associated with caudal regression syndrome. It can lead to oligohydramnios that significantly compromise ultrasound evaluation of the fetus.

Additional benefits of magnetic resonance imaging in the detection of fetal anomalies related to gestational diabetes

Most fetal anomalies related to gestational diabetes can be detected by ultrasound, especially in fetal cardiovascular system. Fetal echocardiography provides both spatial and temporal information, which is very important to make a diagnosis of cardiac disease in utero. Ultrasound is also a great imaging modality for following up the progression of fetal cardiac disease. MRI may complement the ultrasound when certain fetal conditions related to maternal diabetes



Figure 42.3 Magnetic resonance image of a second-trimester fetus with small spina bifida at the lumbosacral level. The fetus is displayed in coronal plane. Multiplanar image display can help associate the defect with its surrounding fetal anatomy.

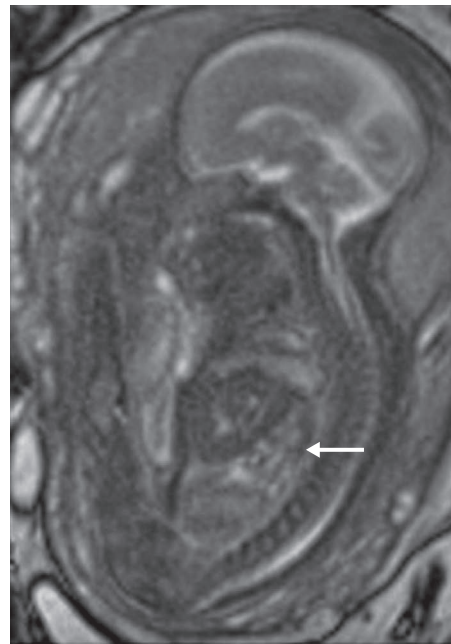


Figure 42.5 Magnetic resonance (MR) image of a second-trimester fetus with dysplastic kidney displayed in sagittal plane. Fetal kidney (arrow) is small and irregular in shape. Multiple hypointense small cavities are found in the subcortical area of the kidney, which is highly suggestive for dysplastic kidney. Note the small amount of amniotic fluid that can affect the image quality of ultrasound. MRI has superb soft tissue delineation even in the presence of low liquor level.

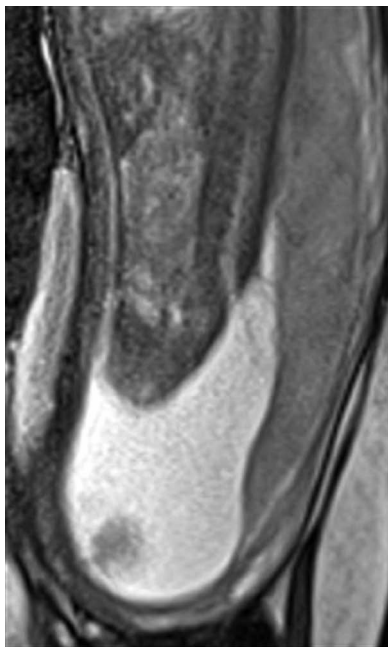


Figure 42.4 Sagittal magnetic resonance image of a fetus with open neural tube defect at the sacral level. Note the protrusion of meningeal sac from the spinal canal at fetal sacral level. No visible spinal cord tissue herniated in this meningeal sac. A favorable prognosis is expected in this low-level lesion without spinal tissue herniation.

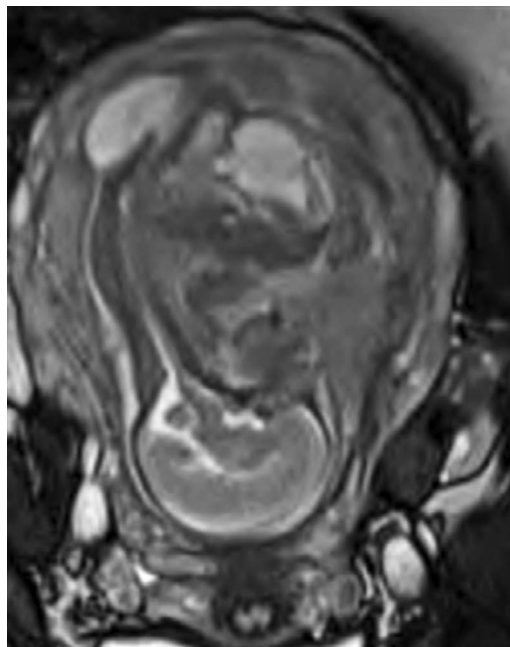


Figure 42.6 Ultrafast sagittal magnetic resonance (MR) image shows a fetus with neural tube defect and cloacal malformation. The cloacal malformation resulted in severe oligohydramnios that makes ultrasound examination suboptimal. MRI is a second-tier imaging modality in this case, when limitation of ultrasound is encountered.

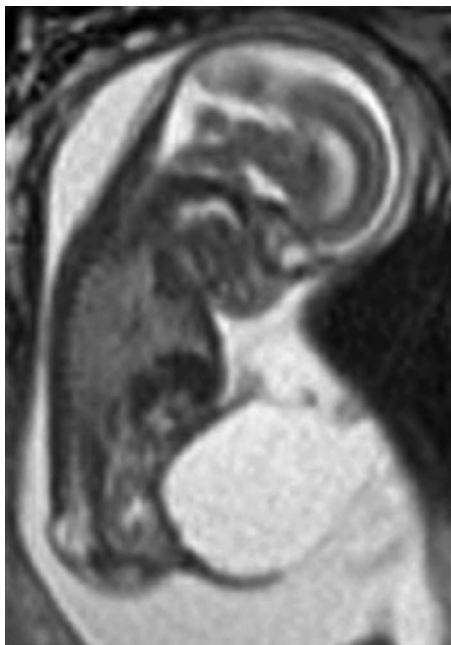


Figure 42.7 Sagittal magnetic resonance image of a second-trimester fetus with a large omphalocele. Note that this fetus also had small spina bifida at the sacral level with the skin covering the defect (closed neural tube defect). No hindbrain herniation is noted.

mellitus are encountered. Examples of these conditions are as follows:

1. Fetal spina bifida with suspicion of hindbrain herniation
2. Maternal morbid obesity precluding adequate ultrasound examination
3. Oligohydramnios precluding adequate ultrasound examination

One of the most unique benefits of MRI study in the fetus is the detailed evaluation of NTD. Fetal NTDs are detected by ultrasound. Direct sonographic finding of NTD is vertebral defect. Indirect sonographic findings, such as ventriculomegaly or Arnold–Chiari type II malformation, can raise a suspicion that lead to a final diagnosis. MRI can confirm the presence of NTD, especially in small lesions, as shown in Figure 42.3. Defect level can be clearly visualized, as in Figure 42.4. MRI can help detect associated anomalies that can significantly impact the prognosis, especially when the liquor volume is low or when maternal adiposity precludes adequate ultrasound examination, as shown in Figures 42.5 and 42.6. It is not uncommon for a fetus with NTD to have multiple malformations. MRI can help demonstrate these associated malformations with a much better clarity, as shown in Figure 42.7. This benefit of MRI is important for prenatal counseling, especially now that in utero surgical repair is possible. The invasiveness of open fetal closure of the NTD that put a significant risk to the mother may not be justified if associated serious malformations are found.

In order for fetal NTD to be adequately assessed with MRI, basic knowledge of fetal structure as it appears on the MRI is crucial. T2-weighted MRI is preferred to visualize fetal brain, spinal cord, and their integuments. The comparison between T1- and T2-weighted images for spina bifida is shown in Figure 42.8. Fetal skull usually shows hypointensity, or “dark” signaling, on T2-weighted images. The vertebrae also show hypointensity. Intervertebral discs show hyperintensity, or “bright” signaling. The spinal canal shows hyperintensity because it is filled with cerebrospinal fluid. The spinal cord can be seen as a structure with hypointensity signaling. The relationship between fetal spinal cord and its canal, the defect of vertebral column, and the presence or absence of skin covering can be depicted with MRI, as

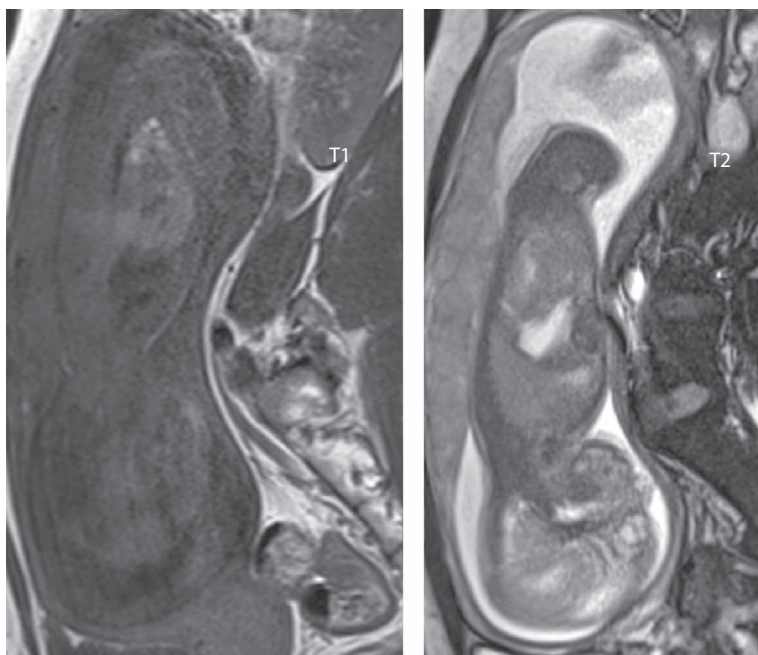


Figure 42.8 Comparison between T1- and T2-weighted sagittal fetal magnetic resonance images. Note that T2-weighted image provides a clearer tissue definition for the fetal central nervous system compared to the T1-weighted image.

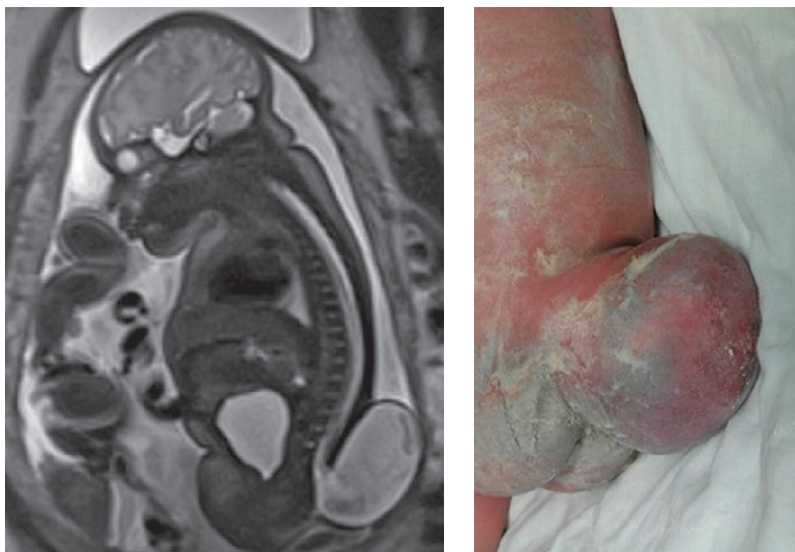


Figure 42.9 Sagittal magnetic resonance (MR) image of a large spina bifida at the lumbosacral level. Note the continuity of the spinal canal into the meningeal sac. The sac did not contain spinal cord tissue. The skin covering the defect is visible on the MR image. Postnatal image of the same infant shows a large defect with full skin cover (closed neural tube defect).

shown in Figure 42.9. Axial cut at the defect level can demonstrate the presence or absence of neural tissue in the sac, as shown in Figure 42.10.

NTD is actually a broad variety of malformations related to failure of closure of neural tube. It can be categorized into open and closed defect. Common open NTD include rachischisis and myelomeningocele. Rachischisis is the most severe form of NTD and is invariably lethal. The absence of an extensive segment of vertebral column leads to a significant exposure of neural tissue. The more common form of open NTD is myelomeningocele. Open NTD, as shown in Figure 42.11, is almost

always found with Arnold–Chiari type II malformation. This is a herniation of the brain stem, the cerebellar vermis, and the fourth ventricle through the foramen magnum due to loss of pressure from leakage of cerebrospinal fluid. The degree of cerebellar herniation is related to seizures, bladder dysfunction, and ambulation restriction.²² Cerebellum and other intracranial structures in the posterior fossa have limited visibility from standard ultrasound examination. MRI can yield more details in the posterior fossa due to its superb soft tissue contrast, as shown in Figure 42.12.²³ Associated higher cerebral abnormalities, as a consequence of NTD, can also be clearly demonstrated with MRI, as shown in Figure 42.13.

Spina bifida (the so-called meningocele) is a common fetal malformation of the CNS. It can cause a significant neurological handicap. In utero surgical restoration of meningocele has been increasingly offered after the result of a randomized trial of prenatal versus postnatal repair of myelomeningocele (MoMs trial) suggested its benefit of decrease postnatal shunt placement and improved motor outcomes.²⁴ Fetal MRI has been advocated in this trial to detect hindbrain herniation, as shown in Figure 42.14. This is used not only for prognostic purposes but also to monitor the possibility of reversal of hindbrain herniation in cases that opted for in utero repair. Comparison of advantages and disadvantages between ultrasound and MRI in imaging of fetal NTD are summarized in Table 42.2.

If defect of the neural tube closure occurs on the cranial end, it will result in meningocele or meningoencephalocele, as shown in Figure 42.15. Most of the time, the defect is on the occipital part of the skull. In meningoencephalocele or encephalocele, there is some brain tissue herniated in the protruded meningeal sac. Encephalocele is associated with a much worse neurological prognosis. Encephalocele can readily be detected on the ultrasound. MRI complements the ultrasound by its ability to detect the herniated brain with higher accuracy. This is particularly important in smaller

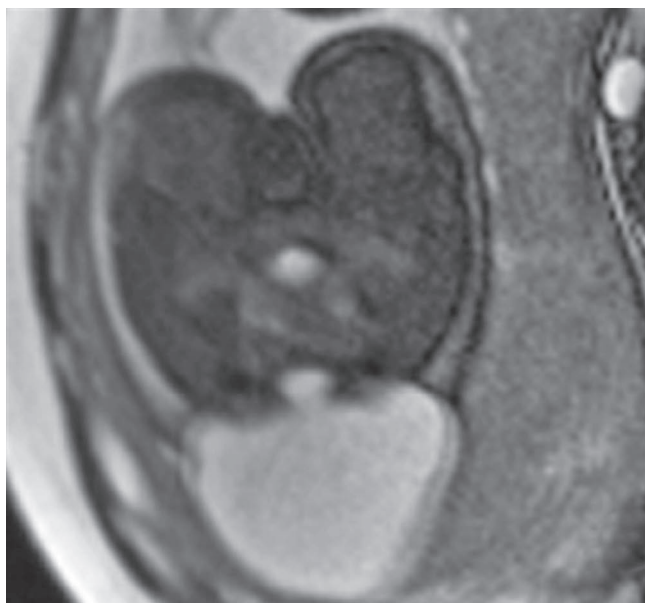


Figure 42.10 Axial magnetic resonance image of the fetus with open neural tube defect at the level of vertebral defect. Note a large protrusion of meningeal sac without spinal tissue herniation.



Figure 42.11 Sagittal magnetic resonance image of a fetus with large spina bifida. Large vertebral defect was seen extending from upper lumbar down to the sacral level. There was no skin coverage, and the spinal cord is fully exposed, as confirmed by the postnatal picture. Also note an obliteration of fetal cisterna magna and dilated cerebral ventricle, which indicate fetal hindbrain herniation.

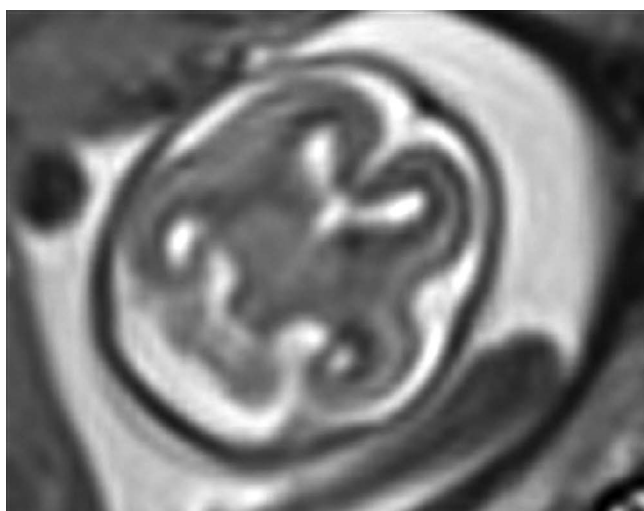


Figure 42.12 Axial fetal magnetic resonance image shows intact cerebellar vermis with cisterna magna. Structures in posterior fossa are harder to visualize with ultrasound.

or deeper lesions, such as lesion in the base of the skull. Associated anomalies of the posterior fossa can be evaluated with higher clarity, as shown in Figure 42.16.

Since NTD is actually a broad spectrum of diseases, the prognosis in neonatal and childhood period can be varied significantly. Larger size of the defect, higher vertebral level, and associated Arnold–Chiari type II malformation are among the important ultrasound prognostic factors for infants born with NTD. The size of meningeal sac itself is not necessarily associated with bad outcomes. Detailed characterization of the fetal cystic lesion is not possible with optimal MRI sequence. Since the presence of neural tissue in the sac can result in worse prognosis, MRI has been advocated

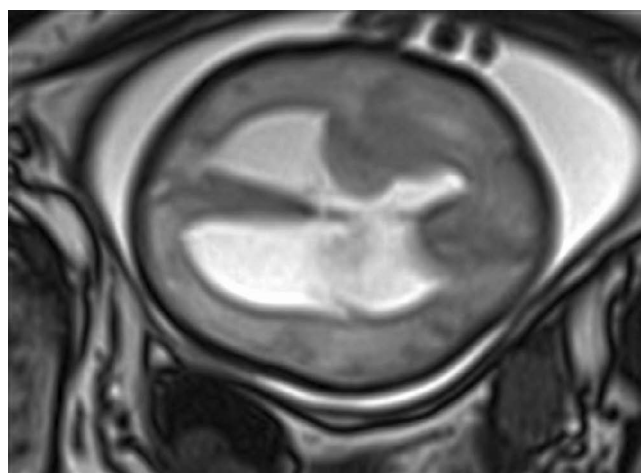


Figure 42.13 Axial fetal magnetic resonance image shows bilateral dilatation of lateral cerebral ventricles in case with large open neural tube defect.

to assess the severity of neural tissue herniation that can lead to a more precise counseling.²⁵

Fetal caudal regression syndrome is usually detected by screening ultrasound examination. It has a typical sonographic finding of a sudden interruption of the spine with absent or hypoplastic sacrum. Associated malformations of the lower extremities, such as hypoplastic limbs and sirenomelia, are common. The legs of the fetus may be consistently crossed. MRI can confirm these ultrasound findings by its clearer soft tissue definition. It can also be used to assess the stenosis of the spinal canal, which can predict the degree of neurological deprivation.²⁶

Cardiac and great vessel malformations are consistently linked to poor periconceptional maternal glycemic control. Most of these cardiac defects can be detected on screening

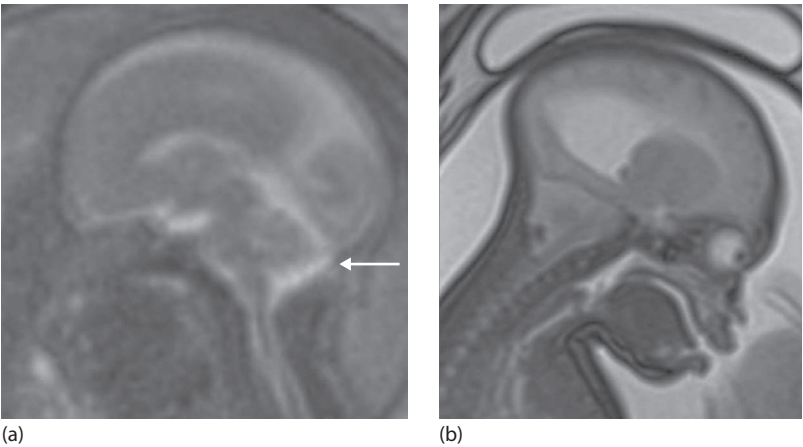


Figure 42.14 (a) Sagittal magnetic resonance images of a fetus with normal hindbrain and (b) a fetus with hindbrain herniation.

Table 42.2 Advantages and disadvantages of ultrasound and magnetic resonance imaging in imaging of fetal neural tube defect

Spina bifida		Ultrasound	MRI
Advantage		First-tier diagnostic imaging for NTD Convenient to follow up on the size and degree of ventriculomegaly Inexpensive Widely available	Second-tier confirmatory imaging for NTD Adequate visualization of posterior fossa Assessment of intracranial involvement and decision for in utero repair Multidisciplinary off-line interpretation for neurological outcomes
Disadvantage		Cannot adequately visualize posterior fossa and hindbrain herniation Cannot adequately visualize associated fetal intracranial pathology, especially when the fetus is not in vertex position Requires an experienced perinatologist to perform and interpret fetal neurosonogram Detect only most severe lesion	Expensive Not widely available Requires an optimized MRI sequences and ultrafast protocol

Abbreviation: NTD, neural tube defect.

fetal echocardiography. Aside from structural defects, fetal echocardiography can also show fetal heart rate, rhythm, and wall motion. MRI is not widely used for the study of fetal heart and great vessel. Because the fetal heart is always moving, the demonstration of fetal cardiac structures using standard fetal MRI sequence is always suboptimal, as shown in Figure 42.17. Gadolinium, a commonly used intravenous contrast for MRI angiography, is contraindicated during pregnancy. Gadolinium can readily cross the placenta and its mutagenic effects are not clearly elucidated.²⁷ However, with the development of MRI sequence optimization, the image quality of the fetal heart and great vessels is improving without the need for intravenous contrast agent.²⁸

In addition to anomalies in the CNS, MRI may have a complementary role in some other fetal malformations related to maternal diabetes mellitus. Fetal renal agenesis related to maternal diabetes mellitus can result in anhydramniotic state. Decreased amount of amniotic fluid makes fetal ultrasound examination suboptimal. MRI is superior to

ultrasound in the detection of fetal malformations when the amniotic fluid is low.²⁹ Anomalies in fetal gastrointestinal system may be better visualized in the ultrasound.

Rationale and application of magnetic resonance imaging in pregnancy complicated with diabetes

Diabetes mellitus is a strong risk factor for congenital malformations, especially those with poor glycemic control in periconceptional period. These women should be offered dedicated ultrasound as the primary imaging modality to detect and to monitor the progress of most fetal malformations related to maternal diabetes mellitus. MRI can complement ultrasound examination, especially in certain malformation, such as NTD. Using MRI as a first-tier screening tool in all pregnancy complicated with diabetes mellitus is currently not advisable.

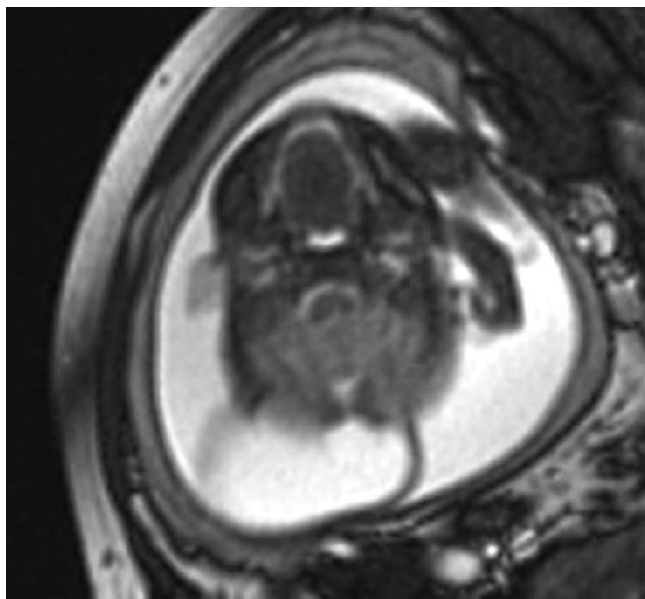


Figure 42.15 Axial magnetic resonance image of a fetus with occipital meningoencephalocele. Note the large defect size with a minimal protrusion of occipital lobe of the brain into the hernia sac.

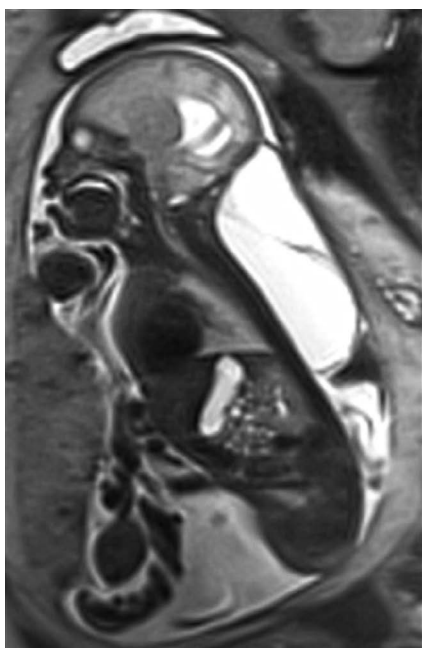


Figure 42.16 Sagittal magnetic resonance image of a fetus with large occipital meningoencephalocele. Note that the sac is large and covered by the skin. Herniation of the brain is noted, along with dilatation of cerebral ventricle suggestive for obstructive hydrocephalus.

Maternal obesity, defined as maternal body mass index over 30 kg/m², is frequently associated with abnormal glucose tolerance and diabetes.³⁰ Obesity is an independent risk factor for congenital malformations due to imbalances in a number of metabolic pathways.⁸ The chance of fetal cardiac malformation in the group of mothers with gestational diabetes mellitus and obesity (BMI $\geq$ 30 kg/m²) was higher than those of nonobese women (odd ratio, OR 2.82).³¹ Excessive

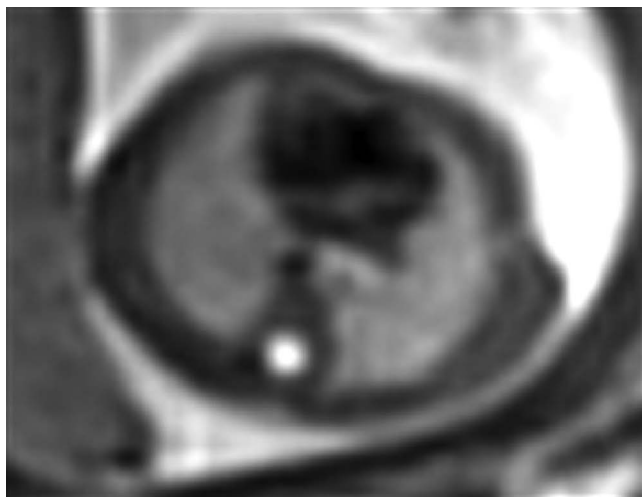


Figure 42.17 Axial magnetic resonance image of a fetus at four-chamber plane. Note that fetal cardiac chambers and great vessels are poorly delineated. The heart is constantly moving, and it requires special MR sequence to adequately demonstrate the structures.

abdominal adiposity can limit the acoustic window for fetal ultrasound examination; therefore, a significant number of fetal anomalies will be missed from the standard ultrasound. It has been estimated that about one-third of women in the United States are obese.³² MRI has no limitation in obesity and can complement the clinical care if fetal anomalies are suspected, but cannot be confirmed, on the ultrasound.

In fact, for an obese diabetic mother, one may choose to evaluate the fetus in the first trimester using high-resolution transvaginal ultrasound. Using transvaginal approach, maternal adiposity and/or bony structures are less likely to compromise the image quality, even in mothers with high body mass index. Figure 42.18 shows the ultrasound

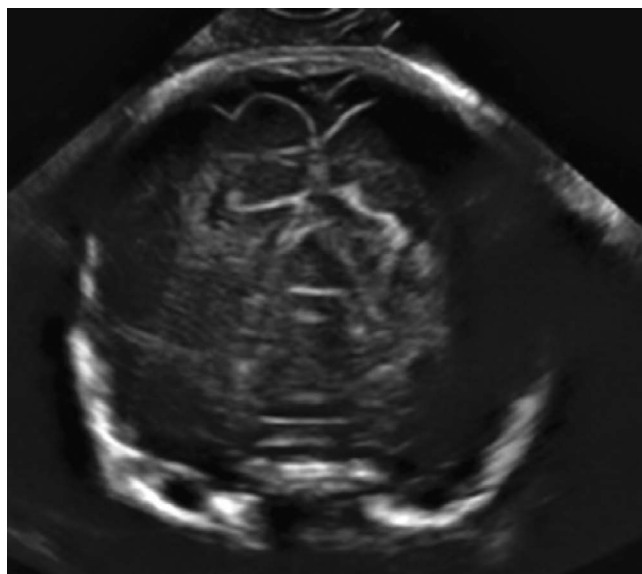


Figure 42.18 Fetal brain can be sonographically examined using transvaginal approach through one of the fetal fontanelles. This approach can obviate the sonographic hindrance by maternal adiposity and fetal skull plate.

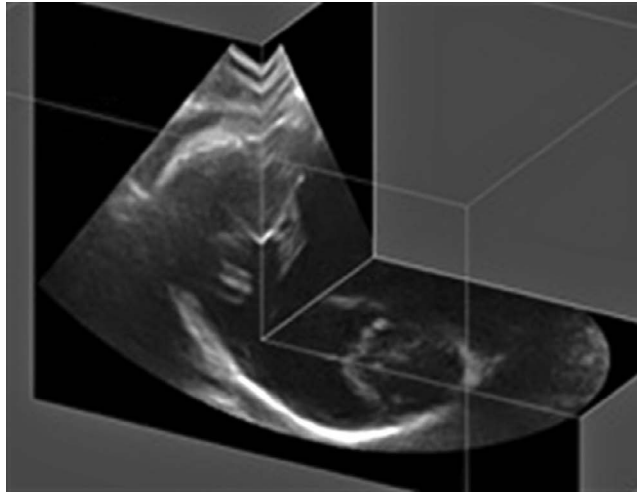


Figure 42.19 An example of using “niche mode”, a novel function of three-dimensional sonography that may improve the quality of fetal brain imaging. This ultrasound picture shows an image of porencephaly (destructive brain lesion) in three-orthogonal multiplanar view.

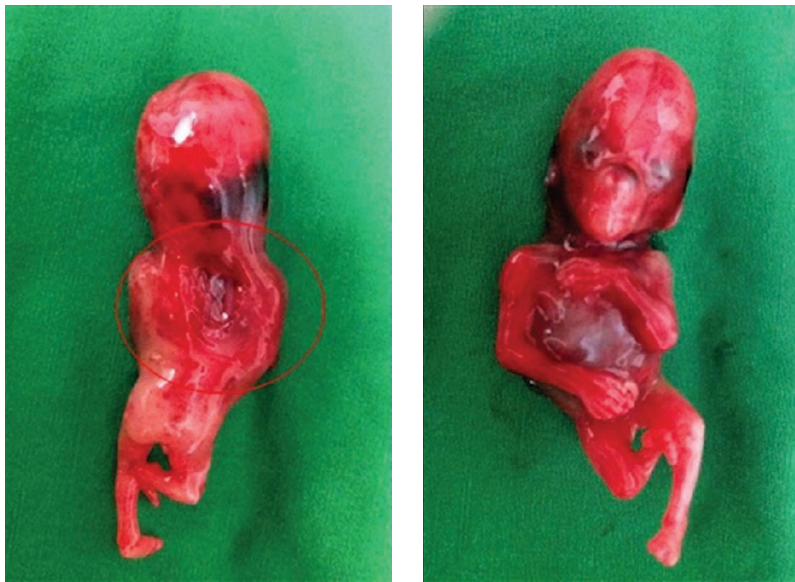


Figure 42.20 Fetus at 11 weeks with spina bifida at the thoracic level diagnosed by transvaginal ultrasound during routine first trimester screening. At this early gestational age, ultrasound is superior to magnetic resonance imaging (MRI) in the diagnosis of spina bifida because of an excessive fetal movement and unclear safety profile of MRI to the first-trimester fetus.

examination of fetal brain using transvaginal approach through fetal fontanel. Ultrasound examination of fetal brain has been enhanced by some novel 3D sonographic modalities, as shown in Figure 42.19. Fetal movement can be readily observed on ultrasound, and it could lead to an early diagnosis of some conditions. Figure 42.20 shows fetal spina bifida at thoracic levels, where the fetal contour is malformed and the movement of lower limbs seen from transvaginal ultrasound examination was limited. On the other hand, fetal MRI is not advisable in the first trimester because excessive movement of the fetus at this stage can cause significant motion artifact on the MRI. Diabetes-related polyhydramnios can increase motion artifact in MRI. It takes several factors to be considered for the choice of optimal fetal imaging modality in each setting.

Summary and future directions

Diabetes mellitus is a common medical condition found during pregnancy. Those with poor glycemic control during the periconceptional period should be offered dedicated screening ultrasound examination. Certain malformations, such as NTD and heart defects, are strongly associated with maternal diabetes mellitus. Ultrasound is the first-tier screening imaging tool of choice in most cases. MRI can confirm the diagnosis in difficult cases, such as in obese mothers or oligohydramnios. MRI can provide more details regarding hindbrain herniation and neural tissue prolapsed in NTD that can be used for a proper counseling for postnatal outcomes. The quality of fetal cardiac MRI has been improving in recent years, and it may be clinically applicable soon

in fetal cardiac assessment.³³ Fetal neurobehavior could be affected by secondary intracranial lesion of NTD that can be studied by ultrasound. Fetal movement can be demonstrated

using dynamic MRI protocol.³⁴ It can be expected that after perinatologists and radiologists gain more experiences with MRI, its fetal indication will be broaden.

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43 Continuous glucose monitoring in pregnancy

Marlon Pragnell and Aaron Kowalski

Introduction

Despite improvements in care, women with diabetes who become pregnant remain at high risk of adverse maternal and fetal outcomes including congenital malformations, perinatal mortality, spontaneous preterm delivery, and macrosomia.¹⁻³ It is now well accepted that exposure to maternal hyperglycemia, in pregnancy complicated by type 1 (T1D), type 2 (T2D), or gestational diabetes mellitus (GDM), is the primary cause of these potentially devastating complications.⁴⁻⁶ Hyperglycemia is toxic from the earliest stages of embryo development with the risk of congenital malformations and fetal death rising dramatically with increasing maternal HbA1c. A recent U.K. population-based cohort study of over 400,000 singleton pregnancies indicated that every 1% increase in HbA1c was associated with a 30% increase in the risk of major congenital abnormality.⁷ Maternal glucose levels equilibrate with the fetal circulation, and this elevated glucose drives insulin secretion leading to abnormal growth acceleration and increased risk of shoulder dystocia, labor induction, and cesarean section. The consequences of these intrauterine metabolic abnormalities may extend well beyond pregnancy as offspring are at increased risk for obesity, impaired glucose tolerance, and the development of T2D later in life.^{4,5,8,9} The risks of maternal complications also increase and include worsening and/or development of nephropathy and retinopathy.^{10,11} Efforts to avoid these devastating complications can be particularly challenging for women early in pregnancy as increased insulin sensitivity often results in a three- to fivefold increase in the rate of severe hypoglycemia, although the consequences on the developing fetus have not yet been determined. Severe hypoglycemia remains the leading cause of death in pregnant women with T1D.

The risks of hyperglycemia and hypoglycemia to both mother and fetus can be mitigated by maintaining tight glycemic control through the diet and insulin and attentive monitoring of blood glucose levels. Fingerstick blood glucose monitoring (also known as self-monitoring of blood glucose or SMBG) is the universally accepted method for monitoring glucose control in diabetic pregnancy, and pregnant women with diabetes are advised to test seven times per day including

around mealtimes and before going to sleep at night. The optimal frequency of finger-stick blood glucose monitoring remains unclear with the Diabetes in Pregnancy Study Group of North America reporting in 2002 that “more measurements are better than fewer, both for patient compliance and in order to assess outcomes.”¹² Continuous glucose monitoring (CGM) is a technology that allows frequent glucose measurements (typically every 5 minutes) and the ability to monitor glucose trends in real time. Although CGM is currently more expensive and mildly invasive, the use of CGM has demonstrated improved glucose control as a stand-alone device, integrated with an insulin pump or ultimately as a component of a closed-loop artificial pancreas system in pilot studies.¹³⁻¹⁶ Already CGM technology has provided unprecedented insights into glucose control in pregnancy and its pathophysiology when complicated by diabetes.¹⁷⁻²⁰ For the pregnant woman with T1D and her healthcare provider, CGM provides a more comprehensive view of how glucose levels fluctuate in response to her meals and other activities and may enable more informed decision making to improve glucose control.

CGM

CGMs in clinical use include devices manufactured by Medtronic (Northridge, CA), DexCom (San Diego, CA), and Abbott (Alameda, CA—not marketed in the United States) (Figure 43.1). These can be worn for 5–7 days and consist of a disposable glucose sensor that is inserted through the skin into the interstitial tissue, a small transmitter that is fixed onto the body surface, and a separate display/storage device. The transmitter contains the power source for the sensor, the amplifier of the sensor signal, and the wireless transmitter. The data generated by the sensor can be stored on the unit for later downloading (termed “retrospective CGM” or “professional GGM”) or transmitted for display on a handheld monitor in real time (termed “RT-CGM”). The disposable glucose sensor consists of a very thin metallic filament coated with glucose oxidase that generates an electric current by catalytic oxidation of glucose in the interstitial fluid. The signal generated is filtered to remove noise, and the corresponding glucose



Figure 43.1 Various types of real-time continuous glucose monitors. (a) Stand-alone devices. From left to right: Abbott Freestyle Navigator®, Dexcom Gen4®, and Medtronic Guardian®. (b) Continuous glucose monitors integrated with insulin pumps. Left: Medtronic MiniMed Paradigm Revel and Right: Animas Vibe.

concentrations are displayed every 5 minutes (typically 288 values/day). Calibration by way of finger-stick blood glucose readings is required at least twice per day. There have been debates in the field regarding the lag between the interstitial fluid glucose from capillary blood. While the physiologic lag is about 5 minutes, there may be additional lag due to diffusion of interstitial fluid glucose across the sensor membrane (1–2 minutes) and signal filtering by the CGM software (3–12 minutes).²¹ This limitation is most evident when glucose concentrations are changing rapidly (>2 mg/dL/minutes) and may be different during a rising vs. a falling phase.

In addition to recent improvements in both accuracy and form factor,²² these devices may include the option to display the data on a smartphone or smartwatch or to share with significant others and caregivers via the cloud.

RT-CGM systems can be set to alert the wearer when glucose values are too high or low via audible and/or vibration alarms. These are particularly useful when the user does not usually perform SMBG finger sticks, such as the first few hours following a meal and overnight—a particularly vulnerable time for hypoglycemic seizures. Alerts are also optional for the rate of glucose rise and fall. To avoid alarm fatigue, these can be customized based on individual safety, tolerance for alerts, and the time of day (using different thresholds during the daytime and nighttime).

Continuous glucose monitors are also available linked with an insulin pump, known as “sensor-augmented pump systems,” in which glucose concentrations are conveniently displayed on the pump’s screen. Significant progress has also been made in the development of future closed-loop artificial pancreas systems where CGM data will be continually relayed to a software controller or algorithm on a smartphone or in the pump that calculates and drives the delivery of the appropriate amount of insulin to maintain glucose control. The first generations, which automatically suspend insulin infusion when hypoglycemia is predicted and resume after the event has been avoided, are already on

the market, and insulin delivery systems are anticipated to be available within the next 2–5 years.

Efficacy of CGM in type 1 diabetes

A number of well-controlled clinical trials in the T1D population have established the efficacy of RT-CGM for improving metabolic control and decreasing time spent in hypoglycemia.^{23–27} The landmark JDRF CGM trial, which studied 322 patients with T1D with baseline HbA1c $>7.0\%$ over 26 weeks, showed that adults aged over 25 years using multiple daily injections (MDIs) and RT-CGM experienced a 0.5% reduction in HbA1c (from 7.6% to 7.1%) compared to patients using MDI and SMBG.²⁸ No significant reduction in HbA1c was observed in subjects younger than 25 years, and there was no significant difference in hypoglycemia in any group. However, the greatest predictor of HbA1c lowering for all age groups was frequency of sensor use, which was lower in younger age groups. In a smaller trial of 129 adults and children who were already well controlled with baseline HbA1c $<7.0\%$, outcomes combining HbA1c and hypoglycemia favored the group using RT-CGM, suggesting it is also beneficial for individuals with T1D who have already achieved good control.²⁴ Similarly, the STAR 3 study, which included 485 subjects who switched from MDI with SMBG to sensor-augmented pump therapy, showed improved HbA1c without increased rates of severe hypoglycemia or diabetic ketoacidosis (DKA) in both adults and children.²⁹

Clinical studies in the nonpregnant diabetic population show that adherence to RT-CGM, with a minimum usage of 4–5 days per week, is a key determinant of improved glucose control. A meta-analysis of six randomized controlled trials (RCTs) consisting of 449 patients randomized to RT-CGM and 443 to SMBG showed that RT-CGM was associated with a significant reduction in HbA1c, which was greatest in those with the highest HbA1c at baseline and who most frequently used the sensors. A best fit regression model showed that for every 1-day increase of sensor usage per week, the effect of RT-CGM vs. SMBG increased by 0.150% (95% confidence interval -0.194% to -0.106%), and every 1% increase in baseline HbA1c increased the effect by 0.126% (-0.257% to 0.0007%).³⁰

A Cochrane review of CGM studies reported until June 2011 performed a meta-analysis of 22 RCTs. The results indicated the benefit of CGM for patients using the device compared with those using MDI and SMBG. After 6 months, there was a significantly larger decline in HbA1c for RT-CGM users starting insulin pump therapy compared with patients using MDIs of insulin and SMBG (mean difference in change in HbA1c level, -0.7% [95% confidence interval -0.8% to -0.5%]). For patients starting with RT-CGM only, the average decline in HbA1c level 6 months after baseline was also statistically significantly larger for RT-CGM users compared to SMBG users, but much smaller than for patients starting using an insulin pump and RT-CGM at the same time (mean difference change in HbA1c level, -0.2%

[95% confidence interval -0.4% to -0.1%].³¹ None of these studies, however, included pregnant women with T1D.

RT-CGM use is not without challenges, and the increased burden perceived by some wearers is an important factor in adherence. Clinical psychologists have identified three major psychosocial themes in responders who have worn RT-CGMs and improved their HbA1c or reduced hypoglycemia. These include (1) coping with frustrations and using self-controlled rather than emotion-based coping when faced with frustrations while using the device; (2) using information in retrospective pattern analysis, not just minute-by-minute data analysis, in glycemic management; and (3) “significant other”/spousal involvement with interest, encouragement, and participation by their loved ones. Indeed, it was noted that CGM use promoted collaborative diabetes management and increased spousal understanding of diabetes especially when planning and managing pregnancy. Both responders and nonresponders expressed body image concerns when using RT-CGM.^{32,33}

CGM in pregnancy: Physiological insights and clinical utility

While many small studies have utilized CGM to gain a deeper understanding of glucose control in pregnancy and its pathophysiology with diabetes, the evidence base for effectiveness in clinical practice is weak, and additional large well-designed randomized CGM trials are required to inform choices of glucose monitoring techniques.³⁴

Physiological insights in normal and obese pregnancy

Prior to the advent of CGM, very little was known even about the “normal” glucose profile in pregnancy. The first study to address this, conducted in 57 nondiabetic pregnant women on 72 hours of retrospective CGM, reported mean and nocturnal glucose levels of 84 ± 18 mg/dL and 68 ± 10 mg/dL, respectively, with a peak postprandial glucose level of 110 ± 16 mg/dL that occurred at an average of 70.5 ± 13 minutes following the start of the meal.³⁵

The first detailed longitudinal CGM profiles of normal pregnancy demonstrated a tendency of postprandial glucose levels to rise even during the course of normal pregnancies with similar caloric intake. These profiles were obtained in a study of 32 women where 72 hours of retrospective CGM data were recorded at 16, 22, 30, and 36 weeks gestation and then at 6 weeks postpartum. Detailed food diaries showed no significant change in caloric intake, and fasting glucose levels did not change significantly although an upward trend was observed at 36 weeks and was highest 6 weeks after delivery. The 2-hour postprandial glucose levels tended to increase throughout pregnancy and then decrease significantly 6 weeks postpartum.

More recently, in a study in 55 normal pregnancies using retrospective CGM over 7 days between 24 and 28 weeks of gestation, the area under the curve of hyperglycemic

excursions was found to better correlate with birth weight percentile than from a single glucose value from a 1-hour oral glucose challenge test.³⁶

CGM has also provided insights into maternal glycemia in obese pregnancies; however, these have been limited by the relatively small numbers and short duration of retrospective CGM data collection. Harmon and colleagues compared 16 obese and 22 normal-weight pregnancies during early (14–18) and late (26–30) gestation. Obese women were found to have higher 24-hour and nocturnal glucose profiles compared with normal-weight subjects and that there was little difference to any of the measured glucose parameters whether the women were on ad libitum or controlled diets.³⁷

Physiological insights into diabetic pregnancy

CGM technology has proved invaluable for understanding the pathophysiology of pregnancy complicated by diabetes. Mazze and colleagues performed a retrospective CGM study in 82 pregnant women of whom 51 were healthy, 6 had T1D, and 25 were diagnosed with GDM. Their study, which also included 21 nonpregnant women, showed healthy pregnancies were characterized by tight glucose control, whereas increasing glycemic variability was observed in the diabetic women. The authors suggested that the use of CGM throughout diabetic pregnancy is “critical if mimicking normal glucose patterns is to be achieved.”¹⁹

Dalfrà and colleagues assessed glycemic variability in 50 pregnant women (20 T1D, 20 GDM, and 10 healthy controls) who wore retrospective CGM for 2 days in each trimester of pregnancy. Women with T1D showed higher glucose variability, with a twofold higher risk of hyperglycemic spikes during the day than healthy women or those with GDM. The latter have only slightly higher CV parameters than healthy controls.²⁰

Most recently, Law and colleagues applied functional data analysis (FDA) to data from a previously published RCTs in a total of 117 pregnant women with T1D ($n = 89$) and T2D ($n = 28$) who used repeated CGM during pregnancy. They demonstrated that lower, less variable glucose levels in the first trimester and higher, more variable glucose levels in the second and third trimesters were significantly associated with large-for-gestational-age (LGA) babies. Temporal profiles in the first trimester indicated that the lower-average glucose levels associated with LGA were driven by distinct dips in glucose levels midmorning and midevening, whereas higher-average glucose levels associated with LGA in the second and third trimesters were driven by significantly higher glucose levels that occur during the early hours of the morning and afternoon in the second trimester and during late evening in the third trimester. The authors also noted that the magnitude of the transient excursions detected by FDA of CGM were substantively larger than the differences in summary statistical indices of average glucose levels and glucose variability, suggesting that the FDA approach may provide greater sensitivity in the analysis of glycemic control in pregnancy.¹⁷

Clinical utility of retrospective CGM in diabetic pregnancy

Retrospective CGM has been shown to facilitate therapeutic changes as a patient educational tool during T1D and T2D pregnancy. In a trial of 71 women (46 T1D, 25 T2D) where the baseline HbA1c was relatively high at 7.3% (SD 1.2%), improvements were demonstrated in maternal glucose control, birth weight, and the risk of macrosomia. Study participants were allocated to standard antenatal care with or without retrospective CGM. Women in the retrospective CGM group wore the device over four 6-weekly intervals. Women returned to the clinic each time for their data to be downloaded and interpreted with a clinician to guide modifications to diet, exercise, and insulin dosing with a focus on reducing postprandial hyperglycemia. Women who wore the device showed reduction in HbA1c that first appeared between 28 and 32 weeks gestation leading to a sustained HbA1c reduction of 5.8% vs. 6.4% ($p = 0.007$) in controls. The infants of mothers wearing retrospective CGM were found to benefit from a lower birth weight standard deviation score (0.9 ± 2.0 vs. 2.6 ± 1.4 ; $p = 0.05$), lower birth weight percentile (69 vs. 93; $p = 0.02$), and reduced risk of macrosomia (35% vs. 60%; $p = 0.05$) compared to controls.³⁸

A recent study with retrospective CGM in 340 pregnant Chinese women with GDM reported CGM use was associated with better glycemic control and improved pregnancy outcomes with reduced risk of preeclampsia and cesarean delivery, decreased birth weight, and improved neonatal complications. In these studies, the women were guided, through modified dietary, activity, or insulin regimens, to limit their postprandial glucose excursions over 140 mg/dL to no more than 10 minutes/day and duration of asymptomatic hypoglycemia to no more than 30 minutes/day. As a result, more women in the CGM group received insulin regimen than in the routine care group (27.9% compared with 6.9%) and experienced a shorter duration of both hyperglycemia and hypoglycemia.³⁹

GlucoMoms, a large multicenter open-label randomized clinical trial of retrospective CGM study, including a decision and cost-effectiveness assessment, is nearing completion in the Netherlands (TrialRegister.nl NTR2996). This trial is enrolling 300 women with T1D or T2D before 16 weeks gestational age or with GDM requiring insulin therapy before 30 weeks gestational age. Subjects have been randomized to standard care or retrospective CGM with the device being worn 5–7 days every 6 weeks. Based on their CGM profiles, subjects receive dietary advice and insulin therapy adjustments as needed. The primary outcome is macrosomia (birth weight above 90%) with birth weight, composite neonatal morbidity, maternal outcome, and costs as secondary outcomes.⁴⁰

Clinical utility of real-time CGM in diabetic pregnancy

While multiple randomized controlled clinical trials have shown that sustained use of RT-CGM improves glucose control in nonpregnant T1D populations, there remains a dearth of evidence in T1D pregnancy.

The only randomized trial of RT-CGM in diabetic pregnancy reported to date, conducted in Denmark between 2009

and 2011, failed to show improvement in glycemic control or pregnancy outcomes in women with pregestational diabetes.⁴¹ This Danish study randomized 154 unselected pregnant women with T1D ($n = 123$) and T2D ($n = 31$) to either intermittent RT-CGM or SMBG. Participants in this study already had good glycemic control with baseline median HbA1c of 6.7% (range 5.3%–10.7%), and so the primary therapeutic focus was on preventing hypoglycemia. Women in both groups were advised to perform at least seven finger-stick tests daily (before and after meals and before bedtime), and those randomized to RT-CGM were advised to wear the device for at least 6 days at 8, 12, 21, 27, and 33 weeks gestation. Women in the RT-CGM group were additionally encouraged to use the device continuously. However, only 49 out of 76 women (64%) reported using CGM as per protocol, and only 5 women (7%) wore the device near continuously (at least 60% of the time). The baseline HbA1c of 6.7% at randomization improved to 6.0% and 6.1% in RT-CGM and control groups, respectively, at 33 weeks with no apparent RT-CGM benefits on glucose control (hyper- or hypoglycemia) or neonatal outcomes, either in MDI or insulin pump users. Neonatal morbidity was high, with 40% of infants being macrocosmic and 25% of infants being delivered preterm or treated for hypoglycemia. The key recruitment barrier for women entering the trial was identified as allocation to the RT-CGM arm, and adherence was poor. A patient satisfaction questionnaire showed that adherence was limited by inaccuracy compared with SMBG, technical challenges, and skin irritation. Additionally, women experienced up to 12 alarms/day during their first period of RT-CGM use, and one-third of these interrupted sleep.⁴²

The lack of benefit of RT-CGM in this trial may be due to a relatively low baseline HbA1c compared with the retrospective CGM trial by Murphy et al.³⁸ and the RT-CGM trials that demonstrated efficacy in the nonpregnant population.^{28,29} Indeed, the authors noted the lack of HbA1c reduction was more in line with a study on well-controlled nonpregnant patients who saw no additional HbA1c improvement with RT-CGM.⁴³ Very poor CGM adherence may also have been a contributing factor as the meta-analysis suggests near-continuous sensor use (6–7 days/week) in addition to higher baseline HbA1c ($\geq 7\%$) is required for CGM benefit in nonpregnant diabetic population.³⁰ It was also noted that the intervention focused primarily on minimizing hypoglycemia, whereas the primary outcome, macrosomia, is usually associated with maternal hyperglycemia. Women in this trial still had 25% of SMBG readings above 144 mg/dL, with the majority of these presumably due to postprandial excursions. Fine-tuning of carbohydrate intake and prandial insulin has been identified as key to achieving stringent postmeal targets, and therefore more robust carbohydrate-based insulin algorithms and/or regular dietary guidance could have helped women achieve the level of postprandial glucose control necessary to reduce macrosomia and improve HbA1c in the trial.⁴⁴

CONCEPTT, a large international trial of RT-CGM in women with T1D funded by JDRF, is currently underway to evaluate the role of continuous RT-CGM before and during pregnancy (NCT01788527). The trial is enrolling 324 women

with T1D in two parallel studies, one in women planning pregnancy ($n = 110$) and the other in pregnant women up to 13-week 6-day gestation ($n = 214$). The primary outcome is the change in HbA1c from baseline with secondary outcomes that include CGM time in target, episodes of severe hypoglycemia, measures of glucose variability, and quality of life. The baseline HbA1c for eligibility is $>6.5\%$ or $<10\%$ in the prepregnant arm and $>7.0\%$ or $<10\%$ in the pregnant arm. To ensure patients randomized into the study can understand the device and adhere to its use, a key challenge in the Danish study, the CONCEPTT protocol includes a 6-day run in phase during which time women will wear a retrospective CGM. CONCEPTT is anticipated to provide unprecedented details of maternal control from conception until delivery and will be the first trial to evaluate the role of RT-CGM metrics in pregnancy (time in target, time spent above/below target with maternal/fetal outcomes). The study will

also provide the most comprehensive assessment of pump vs. MDI on glucose control before and during pregnancy.

Conclusions

Tight glycemic control in diabetic pregnancy is essential for achieving better maternal and fetal outcomes. Clinical studies have shown that retrospective CGM in pregnancy can improve glycemic control and thereby reduce macrosomia. RT-CGM may further improve control by enabling insulin therapy adjustments in real time; however, more clinical data are needed before its use in diabetic pregnancy can be fully endorsed. CONCEPTT, a large international trial of RT-CGM in pregnant women with T1D, may provide a better understanding of the clinical utility of RT-CGM in improving glycemic control.

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44 Insulin infusion pumps in pregnancy

Ilana Jaye Halperin and Denice S. Feig

Introduction to continuous subcutaneous insulin infusion therapy: Components, evolution, and use in the nonpregnant population

Continuous subcutaneous insulin infusions (CSII), more commonly known as “insulin pumps,” were first developed as a research tool in the late 1970s.¹ Insulin pumps use a battery driven motor to continuously deliver insulin through a subcutaneous port. In an effort to mimic endogenous insulin production by a healthy pancreas, prespecified rates of insulin are infused continuously as the basal rate. The patient, via the pump, delivers spurts of insulin, known as bolus doses, when carbohydrates are eaten. Components of CSII therapy include the pump, which has a battery, motor, plunger, and insulin reservoir, tubing that delivers the insulin from the reservoir to the insertion site, and the insertion port that adheres to the skin and keeps the subcutaneous cannula in place.

Pump technology continues to evolve at a rapid pace, and the options available in North America today include pumps without tubing, glucose meters that communicate directly with pumps via wireless technology, and devices that link with continuous glucose monitors (CGMs) enabling “low glucose suspend mode,” which temporarily suspends the infusion if the patient’s CGM senses hypoglycemia.² Most newer-generation pumps automatically calculate bolus doses based on prespecified insulin-to-carbohydrate ratios (i.e., how much insulin the patient needs to cover a certain amount [grams] of carbohydrate) and insulin sensitivity factors (how much one unit of insulin will lower the blood glucose level) that have been programmed into the pump by the patient and/or caregiver. For the bolus doses to be accurate and effective, however, patients are required to enter their current glucose measured by capillary blood and have a good grasp on carbohydrate counting. Despite these advancements, the elusive “closed-loop” system in which the insulin pump functions as an extracorporeal pancreas and the patient is not required to actively self-manage is not yet available commercially.³

CSII is the therapy of choice for a growing number of patients with type 1 diabetes mellitus (T1DM) because of the flexibility and precision that it offers over multiple daily injections (MDIs). However, high costs and the intensive self-management requirements mean that it is still only used in a minority of patients. A 2012 report from the Australian Institute of Health and Welfare showed that 20% of patients with T1DM used CSII, with more than 50% of the patients being less than 25 years old and 60% of the users being female.⁴ In Canada, a pump costs approximately 7000 Canadian dollars and supplies about 6000 Canadian dollars/year. Increasingly, Western governments are paying for pumps and supplies for patients who are compliant and felt to benefit by their caregivers, and this may increase the use of pumps substantially.

Comparison of CSII to multiple daily injections for glycemic control in the nonpregnant population

A 2002 meta-analysis of 12 randomized controlled trials (RCTs) comparing 301 patients on CSII to 299 patients on MDIs showed that CSII patients had an average blood sugar level of 0.9 mmol/L less (95% confidence interval [CI] 0.5–1.2), a mean A1C of 0.5% less (95% CI 0.2–0.7), and a 14% lower total daily dose (TDD) of insulin when compared to patients on MDI (7.3 unit/day range 4.1–10.6).⁵ It is important to note that these trials were done prior to the widespread use of insulin analogues such as glargine and detemir. The MDI regimens included neutral protamine hagedorn (NPH) insulin and ultralente insulin, both of which are more often associated with nocturnal hypoglycemia and thus possibly limiting the glycemic control that could be achieved. A more recent study comparing CSII and a glargine-based MDI regimen showed no difference in A1C but a significant decrease in glucose variability.⁶ Other commonly touted advantages to insulin pump therapy is the flexibility of basal dosing to target the dawn phenomenon (high fasting blood sugar levels that begin around 4 a.m.), without having to risk overnight hypoglycemia. A number of randomized trials have concluded that with comparable or even improved glycemic

control, CSII is associated with up to 50% less hypoglycemia than MDI.¹ However, the meta-analyses only looked at glucose variability and not hypoglycemia. The Ontario Health Technology Assessment Series reviewed the literature in 2009 and felt there was conflicting data on hypoglycemia in CSII compared with MDI.⁷ One concern for users of CSII is that without any long-acting insulin on board, pump malfunction can quickly result in ketoacidosis. Studies have shown, however, that with proper education and resources, the rates of ketoacidosis are similar between the users of CSII or MDI.¹ The key is that patients who use CSII have access to a needle and syringe so that they can give a subcutaneous injection in the case of pump malfunction. Most pump suppliers will provide a backup pump within 24 hours.

Insulin pumps are generally recommended to any patient with T1DM who has one or more of the following: difficulty with labile (high and low) blood sugars, frequent or severe lows, hypoglycemia unawareness, variable work schedules, intensive exercise program, gastroparesis, or a desire for better control to prevent complications.⁸

CSII therapy is not right for all patients with T1DM. In order to benefit from pump therapy, patients need to be engaged with a team of diabetes educators, be willing to do frequent self-monitoring of blood glucose, count carbohydrates adequately, and be comfortable with the physical aspects of insertion sites, tubing, and wearing a pump. In Ontario, Canada, the province provides funding only to patients with T1DM who have demonstrated an ongoing commitment to blood glucose monitoring, the safe and appropriate use of the insulin pump, participation in an insulin pump education program, and regular diabetes clinic attendance. If patients do not have hemoglobin A1C measurements done regularly or do not attend visits with physicians and the diabetes education team, they lose their funding.⁹

CSII compared to MDI in the pregnant population

There have been two meta-analyses of RCTs comparing CSII and MDI therapy in women with T1DM immediately prior to and during pregnancy.^{10,11} Interestingly, despite having similar inclusion criteria and search strategies, the two meta-analysis pooled slightly different studies. Most of the studies were done in the 1980s and 1990s, consisted of very small sample sizes and were of poor methodological quality. The Cochrane meta-analysis¹⁰ of 5 trials and 154 pregnancies did include one study done in 2005; however, this was only published as an abstract and results are no longer available online. The final results for the Cochrane meta-analysis showed no significant difference in maternal outcomes of cesarean birth (risk ratio [RR] 1.09, 95% CI 0.66–1.77), maternal hypoglycemia (RR 3.00, 95% CI 0.35–25.87), or maternal hyperglycemia (RR 7.00, 95% CI 0.39–125.44). Also no significant differences were found in perinatal mortality (RR 2.33, 95% CI 0.38–14.32), macrosomia (birth weight greater than 4000 g) (RR 3.20, 95% CI 0.14–72.62), fetal anomaly (RR 1.07, 95% CI 0.07–15.54), or small for gestational age (RR 1.40, 95% CI 0.10–18.71).¹⁰ Similarly, the

American Journal of Obstetrics and Gynecology meta-analysis of 6 studies with 107 women on CSII and 106 women on MDI showed no significant difference in pregnancy outcomes and glycemic control between users of MDI and CSII. Higher number of ketoacidosis episodes and diabetic retinopathy was found in the CSII group but did not reach statistical significance.¹¹ In their discussion, both authors stressed the need for large, multicenter, RCTs that also assessed the quality of life and cost-effectiveness.

Unfortunately, since that time there have been no further RCTs. Since 2007, over six observational studies have been published.^{12–18} None show a significant difference in patient important outcomes such as cesarean delivery and perinatal morbidity or mortality. One study showed significantly higher Apgar scores in babies born to mothers who used CSII during pregnancy.¹² Two studies showed a lower HBA1c (6.2% vs. 6.5% $p = 0.02$ ¹⁴ and 6.4% vs. 6.8% $p = 0.002$ ¹⁹) and lower insulin doses at parturition. Chen et al. showed a higher rate of diabetic ketoacidosis in the CSII group (13% vs. 2% $p = 0.04$) and neonatal hypoglycemia (35% vs. 13% $p = 0.01$).¹⁷ However, Kallas-Koeman et al. showed no difference in the rate of DKA or hypoglycemia between women on MDI and on pump. They did show a higher rate of large-for-gestational-age babies born to women on pump; however, the study was not powered to determine if this was a true association or due to some unknown confounder.¹⁹

The current body of evidence suggests that pumps can be safely used in pregnancy. Similar to the literature in the general population, it remains unclear if pump therapy offers significant benefits over MDI in terms of hard outcomes such as diabetes complications, severe hypoglycemia, and pregnancy outcomes. However, there are certainly individual patients for whom CSII offers more flexibility, decreased glucose variability, and improved quality of life.

Starting and adjusting CSII therapy during pregnancy

In 2000, Gabbe et al. demonstrated that initiating CSII during pregnancy was safe and effective. They published a retrospective review of three groups: the first started CSII during pregnancy, the second used MDI during pregnancy, and the third started CSII prior to pregnancy; there was no difference in A1C across all three groups throughout pregnancy. Of those that started CSII during pregnancy, 8 of 24 had severe hypoglycemia prior to starting the pump, whereas only 1 had a severe hypoglycemic episode afterward. Compared to no ketoacidosis in those patients on MDI or who started the pump prior to pregnancy, 70% started as an outpatient and 8% (2/24) experienced ketoacidosis. At 12 months postpartum, 95% of the patients continued with CSII and they had a significantly better A1C compared to those on MDI (7.2% vs. 9.1%).²⁰

When starting patients on an insulin pump prior to or during pregnancy, a multidisciplinary team of certified pump trainers, dietitians, nurse educators, and physicians is needed.²¹ A TDD of insulin is calculated from the current MDI regimen and reduced by 10%–20% depending on

the current glycemic control. At the start of pregnancy, basal insulin makes up 50% of the TDD—to get an hourly basal rate, divide this by 24. With increasing pregnancy, bolus rates surpass basal rates in making up the TDD.²² Most patients on CSII have 2–4 basal rates per day to reflect differences in insulin sensitivity throughout the day. These can be preprogrammed if there is a known dawn phenomenon or adjusted after basal rate testing is completed. Basal rate testing involves skipping a meal and refraining from vigorous activity during that time. Frequent capillary blood glucose checks (every 2 hours or more) are required. If the basal rate is appropriate, then the blood sugar level should remain constant throughout the period of testing. If the capillary glucose readings drift up, the basal rate is considered to be too low. If the capillary glucose readings drift down, then the basal rate is too high. The TDD is also used to determine the carbohydrate-to-insulin ratio that is preprogrammed into the pump. The traditional teaching is to divide 500 by the TDD to get a ratio of X g for 1 unit of insulin. For example, a TDD of 50 units/day results in an insulin-to-carbohydrate ratio of 10, meaning that for every 10 g of carbohydrate, 1 unit of insulin is required. This will also be refined over time with postprandial blood glucose monitoring. Finally, the sensitivity factor will be calculated by dividing 100 by the TDD; this will give a correction factor in mmol/L, for example, a TDD of 50 units/day yields a sensitivity factor of 2, meaning that each 1 unit of insulin lowers the blood glucose level by 2 mmol/L.

It is important to provide women with T1DM anticipatory guidance at the start of pregnancy. Regardless of the mode of insulin delivery, they should be aware that their insulin requirements may decrease in the first trimester and then slowly increase after 12–14 weeks, with a leveling off or even a decrease in requirements in the last 6–8 weeks prior to delivery. Titration of insulin doses will be required every 2–7 days to maintain blood sugar levels within the tight targets of pregnancy. Two studies have now shown that bolus insulin doses increase twice as much as basal doses do.^{22,23} One study of 9 women followed closely during pregnancy showed that the average TDD increased from 33 to 94 units. Interestingly, basal rates doubled but bolus doses quadrupled, and the basal/bolus split went from 50/50 preconception to 25/75 at delivery.²² The second study of 26 women showed that the most marked increase in the bolus was seen with breakfast, where the insulin-to-carbohydrate ratio went from median 12 to 13 over the course of the pregnancy.²³

As the consequences of diabetic ketoacidosis in pregnancy are dire to the fetus and insulin precision is paramount, trainers recommend that women change their infusion sites every 48 hours (as opposed to 72 hours in the nonpregnant population), although there is no evidence to back up this recommendation.

CSII in labor, delivery, postpartum, and breastfeeding

While feasible, it is still not common practice to continue CSII during labor and delivery; many centers still favor

the more traditional IV insulin and glucose infusion. One retrospective study from Italy of 65 women on CSII reported that starting at 28 weeks gestation, women and their caregivers were given weekly education on how to manage the pump during labor and delivery.²⁴ Women were instructed to enter a profile B into their pump that was 50% of their lowest basal rate at the end of pregnancy and a profile C that was 0.1 unit/hour. If women were in good metabolic control leading up to the early stages of labor, they were instructed to continue with their usual basal rates (profile A) until the initiation of anesthesia or the beginning of active labor at which point they were to switch to profile B. If they had a low blood sugar level (<3.8 mmol/L), they were to switch to profile C until the BG returned to normal. If the blood glucose level was about 7.8 mmol/L, a correction bolus of 0.5–2 unit was administered. If the blood sugar level was above 10 mmol/L, CSII was stopped and IV insulin was initiated. The average blood glucose level across the 65 women was within the target of 3.8–7.8 mmol/L, regardless of mode of delivery; none of the women experienced a significant hypoglycemia (<2.8 mmol/L) or needed to switch to intravenous insulin. Neonatal hypoglycemia occurred in 17% of the deliveries; all were preterm.²⁴ The authors concluded from this study that CSII can be used safely during labor and delivery in highly motivated patients. It is worth noting that in this protocol, the upper target of 7.8 mmol/L is higher than the target recommended by some guidelines, for example, the 2013 Canadian Diabetes Association Guidelines, which recommends a target of 4.0–7.0 mmol/L to prevent neonatal hypoglycemia (grade D, based on observational data and no prospective, controlled studies).²⁵ The American Diabetes Association makes no recommendation on target blood sugar levels intrapartum. The National Institute for Health and Care Excellence in the United Kingdom recommends maintaining the intrapartum blood sugar level between 4.0 and 7.0.²⁶ The patient and physician should be given the option of switching to an intravenous insulin infusion if the patient become medically unstable or unable or unwilling to continue with the pump during labor and delivery. Some pump companies advise disconnecting the pump when undergoing a surgical procedure where electrocautery is performed. Cesarean sections often involve some degree of cautery; however, our experience and that of the Italian center²⁴ is that there have been no reported cases of pump malfunction; this needs to be validated in a larger survey.

Postpartum insulin requirements drop considerably, and women are usually instructed to take between 50% and 75% of their prepregnancy basal rates and decrease to two-thirds of their prepregnancy carbohydrate ratio and sensitivity factor. Breastfeeding should be encouraged, but women should be informed that they may require even less insulin while breastfeeding because the glucose shunts to the breast milk. In a small study of 18 women, those who breastfed used on average 0.2 unit/kg/day compared to 0.3 unit/kg/day in women who did not breastfeed.²⁷

Table 44.1 Advantages to pump therapy over conventional multiple daily injections

- Provides more precision in calculating basal rates and bolus doses that should result in tighter glycemic control.
- Allows for changes in basal rates to account for changes in activity.
- Can adjust basal rate to account for the dawn phenomenon.
- Easier to give boluses for meals and snacks.
- Bolus delivery can be rapid or extended depending on fat and carbohydrate content of meals.
- Absorption of insulin is more reliable.
- Only need to change site every 24–48 hours as opposed to multiple injections daily.
- Allows for pairing with continuous glucose sensor with potential for low glucose suspend feature.

Table 44.2 Disadvantages of pump therapy compared to multiple daily injections

- Patients always have a device attached to them.
- To achieve optimal control, patients need to have skills in carbohydrate counting and must monitor blood sugar levels frequently (this is actually required for MDI as well, but some patients on MDI with fixed carbohydrate content in their meals can achieve good control).
- Pump malfunction can lead to diabetic ketoacidosis quickly.
- More expensive.
- Need to have skills to troubleshoot device when malfunction occurs.
- Requires a multidisciplinary team who are skilled at managing pump therapy.

Conclusions

There is ample evidence that CSII therapy can be used safely in pregnancy; whether it results in improved outcomes for mother and baby over conventional MDI remains unclear. Women on CSII need to be supported by an experienced team of diabetes nurses, dietitians, and physicians and should be seen frequently during pregnancy as titration of basal rates, insulin-to-carbohydrate ratios, and sensitivity factors are required every week or two. Insulin pumps can probably be used safely in labor and delivery with a caveat that labor and delivery nursing staff, obstetricians, and partners should be aware that women can be switched to an intravenous insulin infusion at any time if the situation necessitate this. Postpartum, it is recommended that doses of both basal and bolus insulin be reduced by one- to two-thirds of the pre-pregnancy settings. Breastfeeding should be encouraged, but pump settings may need to be further reduced to prevent associated hypoglycemia (see Tables 44.1 through 44.3).

Table 44.3 Common definitions in pump therapy

Carbohydrate ratio: Expressed as 1 unit of insulin per X g of carbohydrate. Indicates how many grams of carbohydrate are covered by one unit of insulin. Used to calculate bolus dose based on patient's carbohydrate counting. Initially calculated by dividing 500 over the total daily dose of insulin.

Sensitivity factor: Expressed as 1 unit for X mmol/L. Indicates how many mmol/L drop in capillary blood glucose can be expected with one unit of insulin given as a correction bolus for a high sugar.

Bolus insulin: Surge of insulin given for a high blood sugar level or to cover the carbohydrate content of the meal—made up of both the carbohydrate ratio and sensitivity factor and based on the preset glycemic targets.

Basal rates: Slow infusion of insulin usually 0.5–2 units/hour can be adjusted through the day to accommodate changes in insulin sensitivity such as the dawn phenomenon.

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45 Closed-loop insulin delivery in type 1 diabetes pregnancy

Zoe A. Stewart and Helen R. Murphy

Introduction

The complications of diabetes in pregnancy are widely recognized for both mother and infant and include higher rates of congenital anomaly, stillbirth, neonatal death, and macrosomia.¹ These complications can be partially mitigated with good glycemic control and minimization of time spent hyperglycemic.^{2–5}

However, women with type 1 diabetes face a number of challenges in achieving and maintaining tight glycemic control during pregnancy. Hormonal and other factors mean that insulin requirements change with advancing gestation and can be difficult to accurately predict.^{6,7} Despite regular glucose monitoring, intensive insulin therapy, and “safe” HbA1c levels, women with type 1 diabetes spent an average of 10 hours daily with glucose levels outside the recommended range.⁸ Furthermore, women with type 1 diabetes are at particular risk of hypoglycemia during pregnancy,^{6,9–11} and so the benefits of tight glycemic control must be weighed against the increased risk of hypoglycemia.

Advances in technology for glucose monitoring and insulin delivery such as continuous glucose monitoring (CGM), insulin pumps, and sensor-augmented pump therapy offer the potential of improved glycemic control; however, their efficacy in pregnancy and impact on obstetric and neonatal outcomes need further evaluation.¹²

Closed-loop systems use glucose measurements obtained via CGM and a control algorithm to adjust insulin pump delivery in real time. Initial data suggest that closed-loop systems may be able to maintain near-normal glucose levels and prevent nocturnal hypoglycemia in pregnant women with diabetes.^{13,14}

Components of closed-loop systems

Closed-loop systems comprise three components: a CGM, an insulin pump that delivers a continuous subcutaneous insulin infusion (CSII), and a control algorithm that is administered via a computer system (see Figure 45.1).

Insulin pumps in pregnancy

In nonpregnant cohorts, insulin pumps that deliver insulin continuously via a subcutaneous catheter have been demonstrated to achieve better glucose control with less frequent hypoglycemia than is achieved with conventional multiple daily injections (MDIs) of insulin.^{15,16} However, the benefits of pump therapy are less clear in pregnancy. There have been relatively few studies comparing pump therapy with MDIs during pregnancy, and most have been retrospective observational studies examining small numbers of patients. Further, the majority of extant data derive from older studies conducted when clinicians were less familiar with the use of insulin pumps and before the development of rapid-acting insulin analogues such as aspart and lispro that are used routinely in current clinical practice.

Extant literature suggests that use of insulin pumps during pregnancy is safe and achieves similar metabolic and neonatal outcomes as conventional treatment,^{17–25} perhaps with lower rates of small-for-gestational-age infants,²⁶ fewer episodes of hypoglycemia,²⁷ and lower insulin requirements.^{24,27–29}

A 2011 Cochrane Collaboration review of prospective trials of CSII and MDI in pregnancy found a paucity of randomized controlled trials. Meta-analysis of included trials demonstrated a clinically insignificant increase in mean birth weight when CSII was used, but no difference in macrosomia, cesarean section rates, perinatal mortality, fetal anomaly, maternal hypoglycemia, maternal hyperglycemia, or small-for-gestational-age infants.³⁰ Another meta-analysis of 6 studies (107 women on CSII vs. 106 on MDI) showed comparable glucose control and pregnancy outcomes.²³ These studies had very small sample sizes (mean 18 pregnancies per treatment arm) and lacked power to detect differences in maternal/infant outcomes.

However, some observational studies have suggested increased rates of severe maternal hypoglycemia,²⁴ ketoacidosis, neonatal hypoglycemia,³¹ large-for-gestational-age infants, and perinatal mortality²⁶ when insulin pump therapy is used in pregnancy. Given the highly selected patient populations and small sample sizes, the validity and reproducibility of these results are unclear.

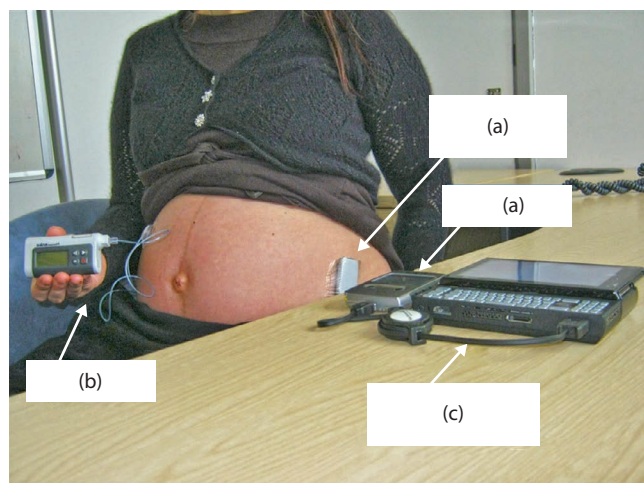


Figure 45.1 Closed-loop systems comprise (a) a continuous glucose monitor (sensor, transmitter, and receiver), (b) an insulin pump, and (c) a control algorithm device.

The majority of insulin pump studies in pregnancy have been retrospective and observational in nature. Women who are commenced on insulin pump therapy often have a longer duration of diabetes and are more likely to already have diabetic complications.^{17,22,28} Therefore, it may be that the increased rates of complications noted previously reflect a more severe glycemic disturbance rather than the mode of insulin delivery.

A retrospective analysis of 387 consecutive pregnancies of women with type 1 diabetes from three Canadian centers found improved glycemic control with pump therapy compared with MDI and no difference in frequency of severe hypoglycemia, diabetic ketoacidosis, or cesarean sections.³² In this study, women on pump therapy started with lower prepregnancy HbA1cs and were more likely to have had preconception care. Women treated with pump therapy were more likely to have large-for-gestational-age infants with a trend toward a higher frequency of neonatal hypoglycemia but no difference in other neonatal outcomes.

Insulin pumps can offer easier titration of doses, which is particularly relevant in pregnancy when insulin requirements are highly variable^{6,33} and increased user satisfaction and quality of life when compared with MDIs.^{25,34,35} Therefore, some benefit may be conferred by using insulin pumps even if glycemic control and maternal–fetal outcomes remain unchanged.³⁶

Given advances in our understanding of physiology, the development of new insulin analogues, and improved practitioner familiarity with the use of insulin pump therapy, many argue that published literature regarding the use of insulin pumps in pregnancy is outdated and that, if used to best effect, CSII may confer benefits including improved glycemic control, similar to what is seen in nonpregnant populations. Large randomized controlled trials using new-generation pumps and fast-acting insulin analogues are needed.

CGM and sensor-augmented pump therapy in pregnancy

It is widely accepted that in order to reduce the fetal impacts of maternal diabetes, periods of hyperglycemia should be minimized. However, in doing so, the risk of hypoglycemia is increased.³⁷ Given that pregnant women are especially prone to hypoglycemia,^{9,11} fear of hypoglycemia can limit the ability to achieve near normoglycemia.

CGM devices comprise a transcutaneous sensor that continuously measures interstitial glucose as a measure of blood glucose and a transmitter that either stores the data obtained by the sensor for retrospective analysis or transmits the glucose values to a receiver so that they can be seen by the patient in real time. CGM, therefore, provides a more detailed description of glucose levels than can be achieved with self-monitoring of blood glucose via finger-stick measurements.

Patients using CGM can see trends in glucose readings and set alerts for hyperglycemia or hypoglycemia that may be missed when relying on clinical symptoms and finger-stick measurements alone.^{7,38} This allows for earlier intervention and potential avoidance of more severe glucose disturbances. In nonpregnant populations, CGM has been demonstrated to reduce HbA1c, glucose excursions, and exposure to hyper- and hypoglycemia.^{39–42}

Sensor-augmented pump therapy involves a patient wearing both a CGM and an insulin pump. The glucose measurements obtained via CGM are entered into the pump (either automatically or manually), and using inbuilt calculators, the pump can recommend appropriate insulin bolus and/or correction doses.

Treatment of type 1 diabetes using sensor-augmented pump therapy has been demonstrated to improve glycemic control and reduce hypoglycemia when compared with treatment using MDIs of insulin or insulin pump therapy alone.^{43–47} The benefits of sensor-augmented pump therapy appear to be greatest with increased sensor use^{42,44,47,48} and in patients who begin with higher HbA1c values.^{39,45,48}

Very few studies have examined the use of CGM devices or sensor-augmented pump therapy in pregnancy. To date, studies have demonstrated that CGM is accurate in pregnancy^{13,49} and can assist in the identification of hyperglycemia and nocturnal hypoglycemia^{50,51} and allow more targeted treatment,⁵¹ which results in lower HbA1c, lower birth weight percentiles, and lower risk of macrosomia.⁵² As in nonpregnant populations, the devices are less accurate in periods of hypoglycemia or when glucose levels are changing rapidly (e.g., during exercise).^{13,49,53}

As a result of ongoing limitations of CGM, current recommendations advise that these systems should only be used as an adjunct tool and should not replace the use of finger-stick blood glucose measurement. An international Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT, ClinicalTrials.gov NCT01788527) is currently evaluating the role of continuous real-time CGM before and during pregnancy.

Another randomized controlled trial (GLUCOMOMS, TrialRegister.nl NTR2996) is evaluating the role of retrospective CGM.

Control algorithms

Proportional integral derivative

Proportional integral derivative (PID) algorithms control insulin administration using a combination of the proportional, integral, and derivative terms.⁵⁴ These terms adjust insulin doses according to real-time glucose levels, the area under the curve between the actual and target glucose levels, and rate of change of glucose to adjust insulin, respectively. The three terms and three individualized constants determine the insulin dose administered. The PID algorithm reacts solely to measured glucose levels and cannot predict future changes in glucose.

Model predictive control

Model predictive control (MPC) algorithms predict future glucose levels based on patients' predicted glycemic responses to insulin and meals.⁵⁵ The difference between the glucose concentration predicted by the model and a preset insulin target is used to determine the rate of insulin delivery. The majority of closed-loop systems currently under investigation use an MPC algorithm because these systems can account for meals, patient-initiated insulin boluses, and individual differences in insulin absorption more easily than systems using other algorithms.

Fuzzy logic

Fuzzy logic models recognize that the same dose of insulin may not always cause the same change in glucose level. These models aim to emulate the decision-making processes and expertise of clinicians and try to account for multiple possible responses to the same insulin dose.⁵⁶

History of closed-loop glucose control

The concept of automated glucose control is not new. In the 1960s, a relatively simple "on-off" system of closed-loop glucose management using intravenous glucose and insulin was developed for use in research settings.⁵⁷ This concept was developed further to incorporate a computational algorithm, and the first commercial closed-loop system, the Biostator (Miles Laboratories, Elkhart, IN), was released in 1977.⁵⁸ This system obtains blood via an intravenous catheter and measures glucose levels before discarding the sample. Blood glucose results are then fed to a computer algorithm that controls administration of intravenous insulin and dextrose. This large device is only suitable for use in closely monitored inpatient settings, and despite multiple attempts, optimal glucose control could not be achieved with available algorithms.⁵⁹

Portable insulin pumps that deliver continuous subcutaneous infusions of insulin have been used in clinical care since the early 1980s.⁶⁰ Since then, pump technology has continued to advance and is becoming increasingly popular. Improvements in insulin pump devices, availability of portable CGM systems (CGMS), development of new quick-acting insulin analogues, and more sophisticated control algorithms have accelerated the development of closed-loop systems.

One approach to closed-loop systems uses intraperitoneal insulin delivery with a glucose sensor either implanted in the superior vena cava⁶¹ or inserted subcutaneously.⁶² This approach has the potential to reduce inherent delays in subcutaneous insulin absorption and deliver insulin in a way that more closely mimics normal physiology. However, intraperitoneal devices are expensive, require surgical implantation, and carry a higher risk of infection and failure than subcutaneous pumps. Intraperitoneal pumps would be inappropriate for routine use during pregnancy.

All other closed-loop prototypes currently being investigated use a subcutaneous glucose measurement device coupled with CSII via a portable pump. This subcutaneous-subcutaneous approach is attractive and likely represents the most feasible model because it is minimally invasive and uses devices that are already commercially available and acceptable by patients.

Progress to date

Low-glucose suspend

The simplest forms of automated insulin delivery are low-glucose suspend systems. In these systems, a message is sent to the insulin pump to temporarily stop basal insulin delivery when the CGM device detects or predicts hypoglycemia and there is no response to warning alarms. This feature has been demonstrated to decrease frequency, duration, and severity of hypoglycemia without causing hyperglycemia or ketoacidosis.^{63–68}

Sensor-augmented pump systems with a low-glucose suspend feature have been commercially available since 2009 (Paradigm Veo and MiniMed 530G with Enlite; Medtronic Diabetes, Northridge, CA). They suspend insulin delivery for up to 2 hours based on measured hypoglycemia but not predicted hypoglycemia. In selected cohorts of high-risk patients, the Paradigm Veo can reduce exposure to hypoglycemia without inducing hyperglycemia.^{68,69}

The effects of low-glucose suspend systems in pregnancy have not been evaluated.

Overnight closed-loop insulin delivery

Approximately 50% of severe hypoglycemic episodes occur overnight and can therefore go unnoticed.⁷⁰ The proportion of severe hypoglycemic episodes that occur overnight is similar in pregnant and nonpregnant populations.⁷¹ However, in pregnancy, the risk of adverse outcome may be particularly

high because counterregulatory responses to hypoglycemia are impaired and severe hypoglycemia is more frequent.¹⁰

One potential early application of closed-loop technology is overnight, when meals and exercise are less relevant, so models for glucose control are less complex. Overnight closed-loop control could also offer substantial clinical benefits including tighter glycemic control and prevention of nocturnal hypoglycemia.

The short-term safety of overnight closed-loop glucose control using an MPC-based algorithm has been demonstrated under research conditions in multiple nonrandomized and proof-of-concept trials^{72,73} and in randomized crossover studies examining a total of 17 children, adolescents, and adults.⁷⁴ In these studies, overnight closed-loop control resulted in better glycemic control and less exposure to hypoglycemia, including after a large carbohydrate meal and alcohol.⁷⁵ Two small pilot studies have demonstrated that overnight closed-loop control using an MPC-based algorithm is safe in early and late pregnancy and can achieve near normoglycemia while reducing exposure to hypoglycemia.^{13,14}

Closed-loop systems using PID and fuzzy logic algorithms have also been shown to be safe and able to maintain good overnight glycemic control in small nonrandomized inpatient studies^{76–78} but have not been tested in pregnancy.

Day and night (24-hour) closed-loop insulin delivery

Ideally, closed-loop technology would be able to achieve and continuously maintain normoglycemia autonomously including during exercise and meal times. However, this remains an ambitious goal. In conventional treatment, patients give a premeal insulin bolus to account for the food they are about to eat, allowing time for insulin absorption and action before glucose from the meal has reached the bloodstream. However, closed-loop control around meal times would rely on changes in interstitial glucose to detect meals, resulting in an inherent delay. These delays, together with the pharmacokinetics of currently available insulins, can result in postmeal hypoglycemia.

Four proof-of-concept trials of day and night closed-loop control without meal announcement demonstrated that closed loop could achieve acceptable glycemic control with low rates of hypoglycemia.^{56,76,79,80} As expected, in fully automated closed-loop control, prolonged postprandial hyperglycemia persisted and postprandial hypoglycemia occurred frequently. Hypoglycemia could be avoided in the first 2 hours after ingestion of a small meal (30 ± 5 g carbohydrate) using an MPC algorithm with a safety constraint that accounts for insulin on board.⁸⁰

As an intermediate step to 24-hour fully automated closed-loop control, some groups have proposed a system that provides day and night closed-loop control but relies on the user to input the timing, and in some cases carbohydrate content, of meals so that the algorithm can calculate appropriate bolus doses.⁸¹ One study found that peak postprandial glucose levels were lower when a premeal priming

insulin dose was given than when a fully automated closed-loop system was used.⁸² Other studies have utilized closed-loop technology for basal insulin delivery but have relied on standard calculation and manual administration of premeal insulin boluses to control meal-related glucose excursions with good effect.^{62,73,83}

A randomized crossover trial of 12 pregnant women examined the use of 24-hour closed-loop glucose control with standardized meals and exercise and manual administration of premeal boluses.¹⁴ In this study, closed-loop insulin delivery achieved near normoglycemia with less frequent severe hypoglycemia than conventional insulin pump therapy.

Although preliminary, data from these studies suggest that stable glycemic control can be achieved with day and night closed-loop insulin delivery. Meal times and exercise continue to pose the greatest challenges for closed-loop systems. Day and night use of closed-loop technology has been demonstrated to be feasible in the outpatient setting⁷² although efficacy has not been established outside of research settings and further studies are ongoing. We previously described a significant gestational delay of approximately 30 minutes in time-to-peak plasma aspart concentration from early to late pregnancy (taking 80 ± 30 minutes in late compared to 50 ± 10 minutes in early pregnancy).⁸⁴ We recently highlighted the marked interoccasion variability of insulin pharmacokinetics during type 1 diabetes pregnancy, showing that while basal insulin delivery was stable, the day-to-day variability of premeal boluses was particularly striking.⁸⁵

Dual-hormone closed-loop systems

Under normal physiological conditions, glycemia is largely regulated by feedback systems using insulin and glucagon. In patients with type 1 diabetes, glucagon function is impaired,⁸⁶ which increases the risk of hypoglycemia. Many argue that an artificial pancreas using both insulin and glucagon to control glucose levels would more closely mimic normal physiology and would therefore be better able to prevent hypoglycemia. Some investigators have demonstrated, under research conditions, that dual-hormone systems can provide good glycemic control and reduced exposure to hypoglycemia.^{87–91} However, current formulations of glucagon are unstable and would not be viable for use in outpatient settings.⁹² There have been no studies of dual-hormone closed-loop systems in pregnant women.

Limitations/obstacles

Sensor delay/inaccuracy

At present, the most viable option for commercial launch of a closed-loop insulin delivery system utilizes CGMs that measure interstitial glucose as a marker of blood glucose. Although these monitoring systems have a level of accuracy that is safe, factors including calibration error and sensor drift can mean that glucose values measured by interstitial

sensors are less accurate than that of finger-stick blood glucose measurements.⁹³

Overestimation of glucose is of particular concern because, if relied upon, these values would lead to excessive insulin doses and potentially hypoglycemia.

Further, the time required for glucose molecules to move from the blood to the interstitium creates a lag of approximately 6 minutes between blood glucose and interstitial glucose.⁹⁴ While some control algorithms account for sensor inaccuracy and the known delay between blood and interstitial glucose, the closed-loop system ultimately relies on the glucose readings obtained via CGMs to make calculations and adjust insulin doses.

Time to onset and peak of insulin activity

As with all automated control systems, there is a time lag between the point at which the algorithm makes a change and the time at which the effect of that change is realized. Most algorithms currently under investigation take into account the time required for delivery and absorption of insulin and the time to peak insulin activity. However, it can be difficult to accurately predict these times because absorption and action times of insulin vary considerably between different individuals and within the same individual at different times.^{89,95}

To avoid accumulation of insulin and subsequent iatrogenic hypoglycemia, closed-loop algorithms need to adjust glucose levels gradually and take into account insulin that has already been administered but is yet to reach its full effect.⁹⁶ Rapid-acting insulin analogues including aspart and lispro have reduced insulin-related time lag^{97,98}; however, it can still take up to 90 minutes to reach a maximum glucose-lowering effect.⁹⁹

Preliminary studies have found that mechanisms including site warming¹⁰⁰ and coadministration of hyaluronidase^{101,102} can accelerate the pharmacokinetics of insulin, and attempts at development of more rapid-acting insulin analogues are ongoing.

Algorithm, meals, and exercise

Algorithms for closed-loop glucose control are now able to achieve near normoglycemia overnight under controlled conditions. However, closed-loop insulin delivery after meals and exercise remains challenging. Where conventional management uses knowledge of food and activity to proactively adjust carbohydrate and insulin doses to potentially

avoid glucose excursions, fully automated closed-loop systems rely on changes in interstitial glucose to identify meal times and exercise before the algorithm can respond and change the insulin infusion rate. This creates an inherent delay. While improvements in algorithms and adjunct tools like heart rate monitors can be used to identify meals and exercise early, without meal or exercise announcement, automated closed-loop systems will always be acting reactively rather than proactively.

Closed-loop systems that incorporate meal announcement or manual premeal boluses will likely provide the most feasible way forward until the challenges of maintaining good glucose control during meal times and exercise without human intervention can be overcome. This is certainly the case in pregnancy where gestational delays in glucose disposal and slower insulin pharmacokinetics mean that human intervention with premeal boluses 15–30 minutes before eating will be required until rapid-acting insulins are available.

Conclusion/future directions

Closed-loop insulin delivery systems have the potential to revolutionize the treatment of type 1 diabetes, resulting in stable glycemic control with minimal patient intervention. This technology could be particularly beneficial in pregnancy, when glucose levels can be difficult to control, the risk of hypoglycemia is increased, and reducing exposure both to hyperglycemia and to hypoglycemia could have lifelong implications for both mother and child.

In nonpregnant populations, closed-loop control can increase the time spent with target glucose levels and reduce frequency and severity of hypoglycemia. Trials are currently underway to explore the feasibility and effectiveness of closed-loop systems for overnight glucose control in outpatient settings over longer periods of time for both pregnant and nonpregnant populations.

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46 Noninvasive glucose monitoring

Itai Ben-David and Pierre Singer

Glucose monitoring

Diabetes mellitus has been recognized for thousands of years, mainly described by its effects on urine. However, it wasn't until circa 1900 that real progress took place in understanding the physiological and pathological basis of the disease.¹ Once insulin was discovered, later extracted from animals and then purified and injected into humans, a treatment became available for what had been a fatal disease, mainly type 1 diabetes mellitus (T1DM). Insulin treatment obviously required monitoring body glucose levels, not the least of which is the risk for hypoglycemia that might be deadly. In the mid-1950s, tablets for urine glucose level monitoring became widely available, soon replaced by strips. During the 1960s, blood glucose level monitoring became available using color strips that reacted chemically and changed their color according to glucose levels. These had to be deciphered using a color chart, meaning they offered estimated rather than exact measurements.² In 1971, the Ames reflectance meter invented by Anton Clemens was the first meter to assess automatically the color change produced by the reagents and offer a point-of-care blood glucose level monitoring system.

Along with the evolution of glucose level monitoring, evidence started accumulating as to the effect of long-term blood glucose level control on related complications and mortality. These beneficial effects were observed in T1DM,^{3,4} type 2 diabetes mellitus (T2DM),^{5,6} and gestational diabetes mellitus (GDM).⁷

Self-monitoring of blood glucose (SMBG) is still the cornerstone of treating insulin-dependent diabetes (types 1 and 2)^{8,9} as well as GDM.⁷ Its beneficial effects have been less consistently proven in patients with T2DM not treated with insulin.¹⁰ However, it is not without problems. Adherence has been shown¹¹ to be less than optimal with the aforementioned regime that requires at least four daily finger sticks. Poor adherence was related to pain and T2DM as well as environmental and psychosocial variables. Obviously, this only underlines the need for better monitoring systems.

The ideal system would be as follows:

- *Accurate*—The demand for this is more pronounced at times of rapid glucose level changes, especially when in the dangerous hypoglycemic regions.
- *Precise*—High reproducibility rate.
- *Fast*—Allowing point-of-care use.
- *Physically comfortable*—Without pain or other local side effects.
- *Easy to use*—Should not impede on daily activities and should not require multiple prolonged calibration phases; its user's instructions should be easy to follow with a comfortable interface.
- *Affordable*—Keeping in mind that T2DM^{12,13} and GDM¹⁴ are more prevalent among persons from low socioeconomic states.

Noninvasive and minimally invasive glucose monitoring: Principles

Given the demands from the optimal monitor, it should be as noninvasive as possible, meaning glucose levels should be measured externally. Attempts toward this objective have been in progress for decades.¹ Obviously, we are not there quite yet; people are still pricking their fingers several times a day. In order to understand why, we need to summarize the methods that have been developed so far to measure glucose levels noninvasively.

The main site used for glucose sensing is the skin. The skin is comprised of the epidermis, which gets most glucose by diffusion, and the dermis, which is supplied by blood vessels.¹⁵ The dermis is the common site for glucose sensing, whether from capillary blood or interstitial fluid. Blood flow to the skin changes with age and disease states. As light passes through the skin, it undergoes absorption and scattering. The epidermis is a light-absorbing layer for light closer to the ultraviolet range, but most red and infrared light passes unchanged, independent of skin pigmentation. In the dermis, the majority of light scattering takes place, mostly due to the optical properties of collagen and elastic fibers.

Shorter wavelengths pass largely unaffected through these fibers as well as the interstitial fluid and are absorbed by the small fraction of tissue that is comprised of blood and cells. This range is referred to as the “optical window” in which red and near-infrared (NIR) light are less absorbed by the other tissue components. Most truly noninvasive glucose monitoring (NIGM) systems are optical in nature and follow these physiological concepts. As variations in skin conditions, such as pigmentation, temperature, hydration, and blood flow, affect the skin’s optical properties, glucose sensing becomes challenging.

A different compartment used for glucose sensing is the interstitial fluid.¹⁶ This is sometimes referred to as minimally invasive glucose monitoring (MIGM), and its measurements are transdermal. Glucose passes from the capillary wall to the interstitial compartment by means of simple diffusion to be later taken up by the cells. This process is affected by many factors, such as metabolic rate, vessel wall permeability, and local insulin levels.¹⁷ When blood glucose level changes, there is a lag time, estimated at 2–45 minutes, between the blood and the interstitial fluids. The relationship between the two compartments, blood and interstitial fluid, constantly changing represents one of the greatest challenges when developing NIGM or MIGM.

Although the skin is the main site of measurement, there are a few others. The oral mucosa was used¹⁸ with limited success relying on the same general principles as with the skin. Other sites used for measurement are the eye and the tympanic membrane. Yet other methods estimate glucose levels from bodily fluids—tears and exhaled breaths. These methods will be discussed in further detail later.

Monitor accuracy assessment

During the 1970s and 1980s, as SMBG became an important tool for managing diabetes, many systems were used to determine accuracy. Correlation coefficients, linear regression slopes, and linear correlation are limited when comparing sets of data approaching unity.¹⁹ Percent deviation is more useful when the difference is consistent across data, but its applicability for glucose measurements is problematic as percentile differences of 20 mg/dL could be negligible in the normoglycemic ranges but very meaningful in the hypoglycemic range. In 1987, William L. Clarke et al. published²⁰ their development of a novel system for comparison of glucose monitoring systems, the error grid analysis (EGA or Clarke EGA). The grid is divided into zones: results that fall within zone A deviate less than 20% and are not in the hypoglycemic range. Zone B represents a higher deviation but one that is still acceptable as it should not affect treatment. Zones C, D, and E represent areas in which results could lead to erroneous, potentially life-threatening decisions. This system was innovative for not only comparing reference and study values but rather emphasizing the clinical implication of the readings. It underwent revision²¹ by Parkes et al. The Clarke EGA was designed at a time when continuous measurements did not exist, and in 2004 a group led by Kovatchev and Clarke proposed the continuous glucose

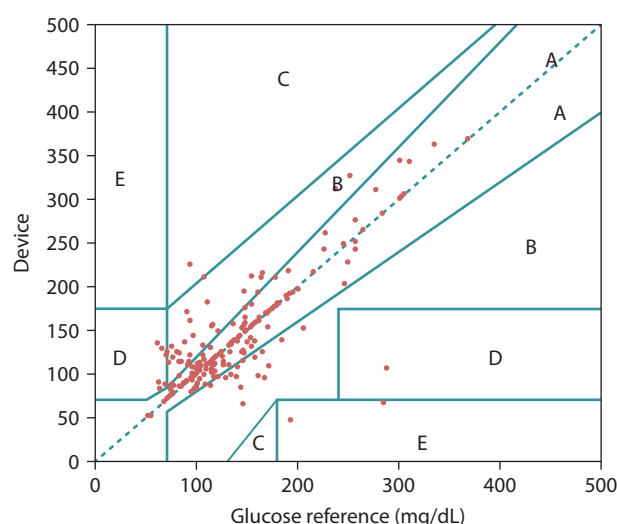


Figure 46.1 An example of a Clarke error grid evaluation. In this example, 74.5% of the measurements fall within area A and 20.7% within area B, giving an acceptable result of 95.5% within these areas. Of the measurements, 1% falls within area E, considered the most hazardous as it would lead to erroneous treatment.

EGA.²² It was evaluated²³ by Wentholt et al. in 2006 and was found inferior in detecting differences compared to accuracy assessment methods such as linear regression and correlation. In general, a perfect accuracy analysis system does not exist, and usually a combination of absolute difference, correlation, linear regression, and Clarke EGA is employed²⁴ (shown in Figure 46.1).

Noninvasive glucose monitoring systems

The appeal of NIGM systems is obvious. NIGM allows patients with diabetes to measure glucose levels without pain, irritation, and risk of infection that are associated with other methods. They allow for tight control of glucose levels, again with the possibility of acting as an afferent limb in a closed-loop system with an insulin pump as the efferent limb. However, technology hasn’t reached that far. Many billions of dollars have been spent trying to reach this goal but with very little to show. There are few noninvasive or minimally invasive systems in the market, and their accuracy and reproducibility levels are generally low. Financial pressure and the urge by the diabetic population sent some of these sensors to the market too early and without a thorough clinical evaluation in different disease states. Dealing with such a technology- and industry-driven field of research, publication bias is expected to be high. Of the few sensors that were released to the global market, selling was stopped on some due to poor clinical performance placing patients at risk. Glucose levels are rather estimated than measured and the margins of error tend to be wide compared to more invasive systems. We shall discuss many of these systems as it would be impossible to discuss all and

Table 46.1 A summary of transdermal techniques for noninvasive glucose monitoring

Technology	Company/product	Site	Results, drawbacks, status
Reverse iontophoresis	GlucoWatch Biographer (Cygnus Inc.)	Wrist skin	FDA approved in 2001. Poor accuracy, mainly in the hypoglycemic range. Frequent finger sticks for calibration. Discomfort associated with its use. Withdrawn from market 2007.
Skin suction blister	Experimental, University Hospital of Aarhus	Volar forearm	Infection risk (low). Fair reliability but increased lag time in six type 1 diabetic patients in 1995.
Sonophoresis	SonoPrep, Sontra Medical	Skin	In 2000, large variability between patients and sites. Improved model with acceptable results in 2004.
Bioimpedance spectroscopy	Pendra (Pendragon Medical Ltd.)	Wrist skin	Pendra was released in 2003 but soon withdrawn due to poor reliability. Requires a prolonged equilibration process. Results affected by temperature and moisture.
Ultrasound with cymbal transducer array	Experimental, Pennsylvania State University	Skin	Animal models only. Fair results in rats in 2005. Good results in pigs in 2009.
Electroporation	BTX Applications	Skin	Animal models only. Good results in rats in 2008.
Electromagnetic sensing	Glucoband (Calisto Medical)	Wrist skin	Released after preclinical trials in 2005. Accuracy affected by temperature and other blood components. Good safety profile.

as research is still very much going on. We will divide these into transdermal systems, which are generally minimally invasive, and optical systems, which are generally truly non-invasive (see Table 46.1).

Transdermal devices

Reverse iontophoresis

The GlucoWatch® Biographer (Cygnus Inc.), up to its G2 model, became Food and Drug Administration (FDA) approved²⁵ in 2001 as an adjunct to finger-stick testing to improve therapeutic decisions. A hydrogel pad is placed over the skin and left to warm up for 2 hours, a finger-stick test is performed for calibration, and it starts measuring glucose level every 10 minutes. The hydrogel pad is replaced every 13 hours. The device employs reverse iontophoresis: Application of a small current to the skin²⁶ and subcutaneous fluid passes through the skin to an electrode pair. This fluid contains glucose at a level proportional to the subcutaneous tissue. Oxidation of glucose is performed on the pad, allowing for level calculation. Its applicability in monitoring for hypoglycemic episodes was questioned as results were disappointing showing very low sensitivity and specificity in the hypoglycemic range.²⁷ It was also deemed too expensive when compared to SMBG and it did not alleviate the need for finger sticks. Perhaps the most unappealing effect was the skin irritation due to the electric current to the skin that afflicted most of all users. Its manufacture and sales were halted in 2007.

Sonophoresis

Skin permeability is increased using low-frequency ultrasound emitted from the SonoPrep™ (Sontra Medical) device.²⁸ A low current is delivered while the return electrode is held by the patient. A biosensor is coupled to the permeated skin and converts glucose into hydrogen peroxide that in turn is oxidized. The current created is measured, and after a calibration phase, the level of glucose can be estimated. Results in a study²⁹ from 2000 were mediocre with 92% falling within areas A+B on the Clarke EGA. In a subsequent trial in 10 diabetic patients,²⁸ results improved with 95% falling within area A+B with no report of pain or irritation by any of the patients. Since then, no significant advance has been reported.

Electroporation

Electroporation is achieved by applying short electrical pulses to the skin, thus reversibly increasing its permeability and allowing for transcutaneous sampling. Developed by BTX® Applications, it was tested³⁰ on rats only, with all data points within areas A+B on the Clarke EGA. Clinical trials in humans have not been reported.

Impedance spectroscopy

A small current is passed across the skin, and impedance is recorded allowing for an indirect estimation of glucose levels. The Pendra (Pendragon Medical Ltd.) was released to the market after CE approval in 2003. Its use was cumbersome as it required a prolonged equilibration phase, and

a year later, the company filed for bankruptcy.³¹ Its results³² were very poor with only 78.4% of the results falling within areas A+B and an unacceptable 4.3% within the most dangerous area E.

Skin suction blister

This technique creates vacuum over a small area of the skin that leads to the formation of a blister. Fluid from the blister is collected and analyzed. The technique was studied³³ on six T1DM patients. Glucose levels in the fluid paralleled closely with the venous levels but the lag time was unexpectedly long in three of the patients. Since 1995, no new advances have been reported.

Ultrasound with cymbal array

Ultrasound waves permeate the skin and glucose is diffused through. Glucose is sensed through a current that

passes through an array of cymbal transducers. These are specialized transducers with compact structures making them potentially comfortable as carried continuous devices. In 2005, the technique was studied³⁴ on rats with good results. It was later studied³⁵ on 200 lb pigs to show that the technique can be used on human-sized animals as well, and results were promising. However, many of the operating conditions of the cymbal array as well as the correlation of glucose between the different components have not been sorted out. Clinical trials in humans are still awaited.

Electromagnetic sensing

The Glucoband® (Calisto Medical) is placed on the wrist skin where it applies a bioelectromagnetic wave specific for glucose and measures resonance and impedance. Preclinical trials quickly prompted its release to the market in 2005 but since no other data have been published and its sales have long ceased (Table 46.2).

Table 46.2 Summary of optical techniques for noninvasive glucose monitoring

Technology	Company/product	Site	Results, drawbacks, status
Mid-infrared absorption spectroscopy	Experimental, University of Cambridge	Skin	Signal influenced by other blood components. Acceptable results in vitro only in 2003.
Near-infrared spectroscopy	Diasensor (Biocontrol Technology Inc.) TensorTip CoG (Cnoga Ltd.)	Skin, oral mucosa	Highly sensitive but limited by physiological variables. Diasensor was rejected twice by the FDA due to safety concerns. TensorTip CoG combines invasive and noninvasive apparatus. Patented in 2011 and marketed in selected countries for type 2 diabetics in 2012.
Raman spectroscopy	C8 MediSensors	Skin	Promising results in 30 subjects in 2009. CE approval in 2012. Seems to have halted progress.
Occlusion red/near-infrared spectroscopy	OrSense NBM	Base of finger skin	Acceptable results in 23 diabetic patients in 2007.
Thermal emission spectroscopy	Infratec Inc.	Tympanic membrane	Good results in 31 insulin-dependent diabetic patients in 2002.
Photoacoustic technique	Aprise (Glucon Inc.)	Skin	Acceptable results in 62 diabetic patients in 2007.
Optical coherence tomography	Experimental, University of Texas Medical Branch	Skin	Good results in 15 healthy volunteers in 2002. Accuracy limited by physiological changes as well as motion.
Fluorescence	EyeSense	Conjunctiva (long term, surgically placed)	Good results in 28 diabetic patients in 2012. Problematic lag time. Hemorrhage and local reactions.
Fluorescence resonance energy transfer	Experimental, University of Western Ontario	Tears	Discrepancy in tear glucose levels. Tear collection takes 10 minutes, limited in situ potential. Requires external illumination.
Optical polarimetry	Experimental, Texas A&M University	Eye	Animal models only. Excellent results in three rabbits in 2012.
Mass spectroscopy		Exhaled breath	Mixed accuracy reports, mostly unsatisfactory.
Kromoscopy	Experimental, University of Iowa and Ohio University	In vitro tissues only	Good glucose and urea discrimination in vitro in 2000. No in vivo data.

Optical devices

Absorption spectroscopy

Absorption spectroscopy utilizes light of variable frequencies in order to measure changes in refraction (scattering), reflection, and absorbance within the tissue. These are affected by changes in the concentrations of different molecules including glucose. In general, these devices comprise of a light source that delivers radiation at the set frequency and intensity. After passing through, the tissue light waves are sensed by the probe and then processed in the processing unit.

Mid-infrared spectroscopy

Absorption spectroscopy in the mid-infrared (MIR) range (2.5–50 μm) has been used to measure glucose levels according to the changes in the beam of light returned to the device. However, many molecules other than glucose also absorb this light.² As light passage is slow, it is affected by the epidermal molecular structure. There are only in vitro data from a study³⁶ on blood from 28 patients in which glucose level correlated well, but it seems this system is not practical in vivo because of the confounding molecules.

Near-infrared spectroscopy

In contrast, light in the NIR range (0.7–1.4 μm) largely passes through the epidermis unchanged and can therefore provide a molecular picture of the dermis. Different calculations are used to estimate glucose level. However, accuracy is hampered by many factors such as other molecules (e.g., urea), skin pigmentation, temperature, and hydration. A different measurement site is the oral mucosa that is richly vascularized but is impaired by the glucose contained in the saliva.

A few sensors have been released to the market. The Diasensor® (BioControl Technologies Inc.) failed twice to gain FDA approval, and in 2002 its CEO pleaded guilty to tax evasions and fraud practically ending a decade of investments of many millions of dollars in this product. The TensorTip CoG® (Cnoga Ltd.) is a device combining invasive and noninvasive measurements that became available in many countries since 2012. A new technology³⁷ using single-walled carbon nanotubes is showing promise as a continuous noninvasive monitor, but research is still at a preliminary level. As mentioned in the text ahead, NIR technology has also been researched as a screening tool for diabetes.

Occlusion red/near-infrared spectroscopy

Occlusion spectroscopy is based on the fact that blood vessel occlusion changes its physical and optical properties. As glucose levels in the blood increase, it changes the scattering properties (smaller scattering coefficient). The device (OrSense®) employs an annular ring placed on the patient's thumb that contains a pneumatic cuff that inflates to an oversystolic pressure for 2–3 seconds and then deflates causing erythrocyte aggregation. The probe also contains a light source in the red/NIR spectrum and a light detector. The passage of photons to the detector is affected by the glucose level as well as hematocrit concentration. It showed promising result in a pilot study³⁸



Figure 46.2 The OrSense NBM-200 device, using occlusion red/near-infrared spectroscopy. (By courtesy of the manufacturer.)

in 23 diabetic patients before and after a meal with 95.5% of the measurements falling within areas A+B on the Clarke EGA compared to SMBG. However, since 2007 no further data have been published on this device, and it is not commercially available for glucose monitoring (see Figure 46.2).

Raman spectroscopy

Light of a single wavelength (monochromatic) is passed through a tissue. When it interacts with glucose, the energy of the photons is shifted according to the vibrational and rotational energy of glucose, thus providing selective information about the level of glucose. It may differentiate between two similar molecules like glucose and galactose.³⁹ In 2009, it was tested⁴⁰ on 30 human subjects with 387 different site measurements. Results were acceptable with 92% of data points falling within areas A+B on the Clarke EGA. This device from C8 MediSensors has received CE approval in 2012 but since progress seems to have halted.

Photoacoustic technique

This is a different spectroscopy technique. Light passed through a tissue is converted into heat that emits ultrasonic waves caused by local expansion. These are interpreted by the processor to calculate the glucose level. The Aprise™ (Glucon Inc.) device was examined⁴¹ on 62 diabetic patients with 979 paired measurements. Results were acceptable with 94.6% of the points falling within areas A+B on a Clarke EGA. Further research is awaited.

Thermal emission spectroscopy

The site of measurement for this device is the tympanic membrane. The human body emits electromagnetic radiation that stands in relation to spectral distribution. The handheld apparatus analyzes light in the MIR range that is influenced by the body's composition. In 2002, thermal infrared emission characteristics of different glucose concentrations were measured⁴² in 26 patients with insulin-dependent diabetes (T1DM and T2DM). No side effects were reported. Out of

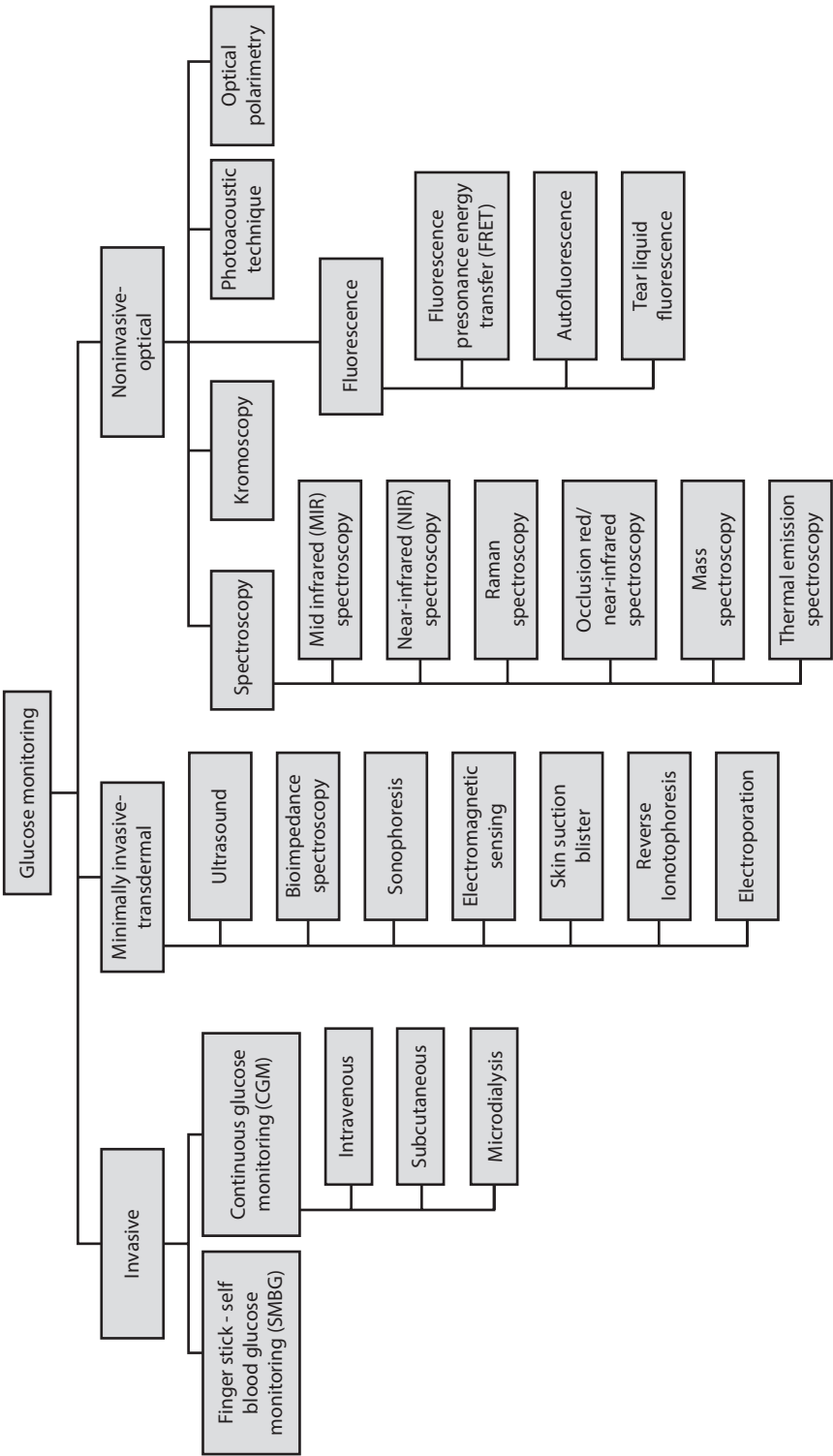


Figure 46.3 Existing and underdevelopment technologies for noninvasive glucose monitoring.

432 paired data points, all fell within areas A+B (97.5% in area A)—excellent results. Despite the good results, 12 years later, this is still the only published data in the field.

Fluorescence and FRET technology

Different molecules in different states emit varying light intensity.² Using the molecule Concanavalin A (ConA) that has four glucose binding sites,⁴³ the level of glucose can be calculated using a competitor such as fluorescein. This technique as a method for glucose sensing has been studied⁴⁴ for over 30 years. Different enzymatic reactions have been used. Most recently, EyeSense® released an implantable glucose monitor that is placed between the eye and the conjunctiva. Studied⁴⁵ on 28 diabetic patients, most patients suffered subconjunctival hemorrhage postoperatively but afterwards only complained of mild discomfort. Reading accuracy was acceptable with more than 96% of the points falling within areas A+B on the Clarke EGA; however, a shift from area A to B was noticed. Lag time still poses a problem of unknown significance.

A different technology is fluorescence resonance energy transfer (FRET). First studied⁴⁶ in 1988, this technique is based on the transfer of energy from donor molecules to acceptor molecules, thereby decreasing fluorescence levels allowing for miniscule changes in the level of molecules to be detected. Studied in preclinical models,⁴⁷ generally a contact lens is used and boronic acid is usually the donor molecule. A few devices have been patented, but many problems still need to be addressed—the longer time it takes for tear collection, the more the need for an external light source and the lack of a predictable relationship between blood and tear glucose levels.

Optical polarimetry

When polarized light hits certain molecules, it rotates. These molecules are called optically active and they can be detected using polarimetry. Using a dual-wavelength optical polarimeter, this technique was studied⁴⁸ in 2012 on nine rabbits employing a contact lens and an external light source, measuring the glucose level within the aqueous humor. Accuracy was very good with 100% of the results falling within areas A+B on the Clarke EGA. These data are still preliminary, and many adaptations will be needed for human subjects as an external light source must be placed directly on the eyelid, causing discomfort and also limiting the continuity of measurement.

Optical coherence tomography

Introduced⁴⁹ in 1991, this technique uses and detects light reflection from tissues combined with light from a reference arm. The device contains a photodetector and an interferometer to achieve a high-resolution analysis of the tissue scattering properties. Studied⁵⁰ in 2002 on 15 healthy subjects undergoing oral glucose tolerance testing, results were in good correlation with blood glucose levels. However,

a fluctuation in data points was observed as a result of motion, limiting applicability, as well as being confounded by parameters such as temperature changes, tissue components other than glucose, blood pressure, and heart rate (see Figure 46.3).

Other forms and applications of noninvasive glucose monitoring

Noninvasive glucose monitors as screening tools

Apart from its place in managing glucose levels in diabetic patients, NIGM is being increasingly investigated as a diagnostic screening tool. The NSEEDS trial⁵¹ used skin fluorescence spectroscopy to evaluate the glycemic response to oral glucose loading and was found to be similar to A1C and FPG for the detection of abnormal glucose tolerance. NIR was examined⁵² on 154 healthy and diabetic subjects, achieving 77.3% sensitivity for the detection of diabetes with 70% specificity, comparable with FPG measurements,⁵³ while alleviating the need for fasting.

Autofluorescence was evaluated⁵⁴ for differentiating normal pregnancies from GDM according to levels of advanced glycation end products; results were disappointing as it could not differentiate between the two groups at time of diagnosis, nor was it able⁵⁵ to diagnose gestational diabetic pregnant women at high risk for complications.

Hypoglycemia monitoring

As said earlier, one of the major pitfalls of most many NIGM systems is their failure to recognize hypoglycemic states leading to delayed or even deleterious treatment. An altogether different approach toward NIGM is not measuring the glycemic level but rather monitoring for the signs of hypoglycemia, mainly the autonomic reactions. This may help deal with nocturnal hypoglycemia, a prevalent⁵⁶ pathological state that can cause seizures⁵⁷ and might even be fatal.⁵⁸ The HypoMon® (AiMedics Pty. Ltd.)⁵⁹ is a chest belt worn during the night that monitors surface ECG and skin bioimpedance. It also includes a radio-frequency transmitter that sends signals to a receiver that can be placed in the same room or an adjacent one. Tested on 52 patients with T1DM, it showed a positive predictive value of only 38%, not yet considered acceptable. Another apparatus is the Gili Medical hypoglycemia noninvasive monitoring system (Gili Medical Ltd.), which contains four sensors that monitor for physiologic effects of hypoglycemia—heart rate (tachycardia), perspiration level (increased), skin temperature (peripheral vasoconstriction), and body movement level (trembling). The monitor is placed on the hand and is connected to a receiver. Tested⁶⁰ on 10 patients with T1DM, it showed high sensitivity and specificity (100% and 85.7%, respectively). This technology is still in development and its design must become less cumbersome. It should be noted that these monitors are limited by many factors that hamper the autonomic reaction to hypoglycemia such as hypoglycemia tolerance and β -blockers.

Exhaled breath analysis

A proposed alternative to finger-stick systems that collects condensed humidity in exhaled breaths for glucose level measurement has been developed.⁶¹ Within 10–20 minutes, enough respiratory secretions (1–2 mL) can be collected for analysis.⁶² Respiratory fluids normally contain low levels of glucose. In pathological conditions such as cystic fibrosis and diabetes, these levels are increased.⁶³ These secretions may serve as a surrogate for blood glucose measurement as blood glucose levels may be estimated by analyzing the glucose level in the secretions, mainly in the pediatric population, but further research is pending.

Continuous glucose monitoring systems

Similar to NIGM but more invasive are the continuous glucose monitoring systems (usually referred to as CGM or CGMS). These are more invasive systems and have consistently shown far better results. Because CGMS are widely marketed, they are discussed in depth in a different chapter. However, they will be shortly mentioned here. Often, NIGM and MIGM are considered forms of CGM, but here they are reviewed separately.

The typical CGM device includes a sensor, sensing glucose in the interstitial fluid or in the blood; a processing unit, wireless or with wires; and a screen displaying the result. When the monitor is accurate and precise enough, allowing a reliable and reproducible safety profile, it can be connected to a fourth element, a continuous insulin pump. This is truly an artificial pancreas (regarding the β -islet function).

In the subcutaneous or intravenous CGM devices, the sensor is placed within the subcutis or a vein where it obtains a continuous reading of glucose level in the fluid. In the earlier models, it was connected by a wire to the processing unit, but the more modern devices are completely implanted and interface with the external controller wirelessly. The sensing process is usually based on glucose oxygenation, and then an assay by optical or electrochemical assay is performed. The reading is transmitted to the display unit (usually by radio frequency). In earlier models, the data had to read retrospectively but the newer models allow real-time CGM. An earlier systematic review⁶⁴ couldn't show significant improvement in treatment targets. A more recent meta-analysis⁶⁵ of six randomized controlled studies evaluating glycemic control in T1DM using real-time CGM showed lower glycated hemoglobin (HbA1c) and lower hypoglycemia rate in CGM users.

The Minimed[®] (Medtronic Ltd.) is probably the best studied system,^{66–68} available in multiple models. It was studied in pregnant women as well,⁶⁹ and its use was associated with a better glycemic control, a lower birth weight, and a reduced risk for macrosomia. It was prospectively studied in 34 gravid patients with GDM⁷⁰ and detected postprandial hyperglycemia as well as nocturnal hypoglycemia better than SMBG. Other widely available systems that have shown good and reliable results are the Dexcom Seven[®] (Dexcom Ltd.) that recently showed⁷¹ improved accuracy and the Freestyle[®] (various models, Abbott Diabetes Care). The latter was studied in pregnant women suffering from T1DM⁷² and was found safe but still not of optimal accuracy. In another study⁷³ in pregnant diabetics, it was found less accurate during moderate exercise. It should also be mentioned that some of the older models of the Freestyle sensors were recalled in the beginning of 2014.

A different approach is microdialysis. A double-lumen catheter is placed within the subcutaneous tissue, and a glucose-free isotonic fluid is transfused continuously over a dialysis membrane. Glucose permeates the membrane and its level is assayed. It can also be placed intravenously in hospitalized patients.⁷⁴ This technique showed⁷⁵ its ability to reduce HbA1c levels in patients with T1DM. The GlucoDay[®] (Menarini Diagnostics) is the main commercially available model, studied⁷⁶ since the early 2000s.

Conclusions

The place for NIGM is obvious—a painless system that can measure glucose levels and guide treatment could dramatically improve the quality of life of diabetic patients and reduce long-term organ damage. Results, however, have been generally disappointing, especially when compared to the more invasive CGMS that have consistently shown good results and are becoming an integral part in the management of diabetes, especially insulin dependent. This is certainly not for lack of investment. Billions of dollars⁷⁷ have been spent on research with very little to show. Devices released to the market with great promises, especially in the lay press, were later quietly withdrawn due to poor postmarketing results. Is there a future for NIGM systems? In the authors' opinion, it remains unclear. It is clear, however, that devices must stand more rigorous testing before being released into the market. Only time will tell whether advances in basic science could translate into accurate, precise, affordable, comfortable, and easy-to-use systems that could become an integral part in the diagnosis and treatment of diabetes.

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47 Reproduction and its impact on health and disease

Sara Ornaghi and Michael J. Paidas

With the exception of the stomach, there is no organ that holds such numerous ramifications of sympathy with other organs as the womb.

J.M. Good (1825)

Introduction

Women's reproductive health is intimately linked with their overall physical and mental health. The vitality and performance of women's reproductive axis—as revealed in patterns of menstruation, fertility, and pregnancy—yield important information about subclinical disease trajectories. Many of the factors that contribute to coronary heart disease, stroke, and cancers—inflammation, vasculopathy, angiogenesis, thrombosis, insulin resistance, and altered endocrine profiles—also underlie aberrant menstrual patterns, female infertility, pregnancy complications, and adverse pregnancy outcomes such as preterm delivery (PTD) or fetal growth restriction.¹

It has long been understood that pregnancy complications are important for the lifelong health of offspring in the context of fetal programming but much less appreciated that these complications also have key implications for the long-term health of the mother.¹ Indeed, pregnancy complications may be the first warning that a woman is at an elevated risk for future cardiovascular disease (CVD).² An accumulating body of research has shown that common pregnancy complications, including PTD, fetal growth restriction, preeclampsia, and gestational diabetes mellitus (GDM), predict the future risk of chronic diseases in women, including CVD, diabetes mellitus (DM), and breast cancer.^{1,3} Of note, a high proportion of women will, in the course of their reproductive career, have at least one of these pregnancy adverse outcomes. Indeed, the prevalence of any one of these conditions in any given pregnancy ranges from 2% to greater than 12%.³ Because of the actual magnitude of this problem, an in-depth insight appears mandatory.

Implications of pregnancy history on subsequent women's health

CVD risk

Globally, one of three women dies from CVD.⁴ In response to the growing appreciation that many preventive efforts start too late to be effective, there has been a call for “primordial prevention”—prevention of the major CVD risk factors themselves.^{5,6} In this context, pregnancy complications have the potential to be effective CVD risk “stress tests” to identify women who would most benefit from primordial or primary prevention efforts to reduce CVD risk.

In a large retrospective cohort study in more than one million women in Canada, the risk of premature CVD has been shown to be strongly related to the severity of metabolic disturbances that have occurred during pregnancy.⁷

A key factor underlying CVD is the metabolic syndrome. The metabolic syndrome is a spectrum of metabolic abnormalities associated with insulin resistance, which is manifest as relative hyperglycemia, hyperlipidemia, and disturbance of coagulation. The normal physiological response to pregnancy represents a transient excursion into a metabolic syndrome, with a relative degree of insulin resistance, definite hyperlipidemia, and an increase in coagulation factors.^{8,9} Normal pregnancy also involves upregulation of the inflammatory cascade.¹⁰ Such upregulation in nonpregnant women has recently been recognized as an independent predictor of cardiovascular events and DM.¹¹ Such metabolic responses, which are the result of the pregnancy-related hormonal changes,¹² could be considered as “stress” tests of maternal carbohydrate and lipid pathways and vascular function. In this way, adverse pregnancy outcomes may be indicators of an increased risk of metabolic and vascular diseases in later life (Figure 47.1).

Recently, a review analyzing the evidence for associations of parity and common pregnancy complications (low birth weight, PTD, hypertensive disorders of pregnancy, and GDM) with future CVD risk has been published. Physiological mechanisms that might underlie these

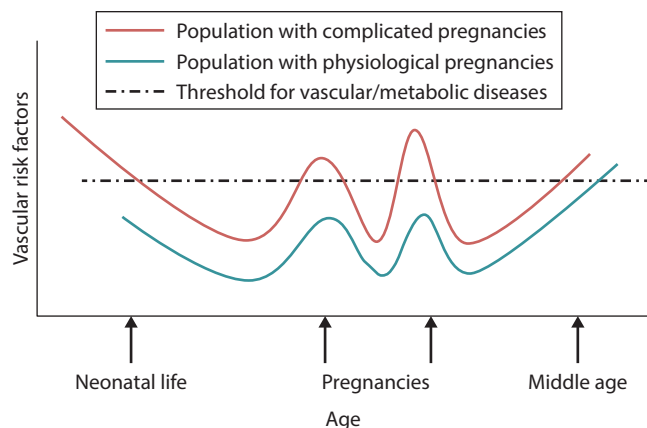


Figure 47.1 Vascular risk factors and metabolic syndrome of pregnancy. (Adapted from Sattar, N. and Greer, I.A., *Br. Med. J.*, 325, 157, 2002.)

associations and implications for future research and for healthcare design and policy have been also investigated.³

Risk factors for vascular disease are identifiable during excursions into the metabolic syndrome of pregnancy.

Parity

The association between parity and later CVD has been investigated in several studies.^{13–16}

To date, the largest study published included 1.3 million women (included in the Swedish registry data) with a median follow-up time of 9.5 years.¹⁶ Parity was shown to be associated with CVD in a J-shaped fashion, with two births representing the nadir of risk. Specifically, women with 0 and ≥ 5 births had multivariable-adjusted hazard ratios (HRs) of 1.11 (95% confidence interval [CI], 1.09–1.14) and 1.57 (95% CI, 1.52–1.64), respectively, as compared with women with 2 births.

Investigation of the association between number of children and paternal CVD risk has helped in gaining a better understanding of the parity associated with maternal CVD risk. Indeed, similar associations for mothers and fathers would suggest that the association between parity and maternal CVD is not causal but is more likely a result of confounding by socioeconomic position and/or behaviors related to child-rearing and shared by both parents. Three reports have endorsed this hypothesis.^{17–20}

Birth weight

Birth weight is the conventional measurement used to indicate how well fetal growth has succeeded. However, it is dependent on gestational age and to a lesser extent on gender. In this respect, the fetal growth degree can be defined as birth weight standardized for gestational age and gender, with small for gestational age (SGA) and large for gestational age being the two extremes.^{21,22} Another measurement of fetal growth is the physical shape of the newborn, the ponderal index, which is an indicator of infant leanness or obesity, parallel to body mass index (BMI). This can be construed to represent the fetal growth mode, which is also dependent on gestational age. The standardized birth weight may be regarded as

the result of constitutional determinants and external factors that influence fetal growth throughout pregnancy, whereas the ponderal index may reflect restriction or acceleration of nutritional status in the last part of pregnancy.²³

Offspring birth weight has been reported to strongly predict maternal life span.^{24–28} One meta-analysis has calculated that, for every standard deviation (roughly 500 g) higher birth weight of the firstborn child, maternal CVD mortality is decreased by 25%.²⁴

A twofold increase of the maternal CVD incidence and mortality is reported for pregnancies complicated by having low-birth-weight infants (<2500 g), whose incidence is nearly 8%.^{24–26,28} Further, adjustment for cigarette smoking decreased this risk only modestly, and no correcting effect was identified for prepregnancy BMI.^{29,30} The presence of insulin resistance, hypertension, and inflammation likely underlies this increased risk.²⁷ However, as previously mentioned, the basic birth weight is not so accurate as standardized birth weight and ponderal index in evaluating actual fetal growth. Therefore, Lykke et al. investigated the relation between the standardized birth weight by gestational age and gender and the ponderal index and the mother's subsequent mortality and cardiovascular morbidity.³¹ The authors showed that the risk profile for the standardized birth weight and subsequent maternal death progressively increased with decreasing fetal growth, peaking at -3 SD (HR 2.75; 95% CI, 2.37–3.19) compared to the median. Further, the risk profile for subsequent DM by standardized ponderal index appeared to rise with increasing fetal growth and to peak at $+3$ SD (HR 17.8; 95% CI, 15.0–21.0). The authors concluded that fetal growth is to be considered a pivotal marker of subsequent risk for premature death, CVD, and DM in the mother. Specifically, since higher estimates were identified for standardized birth weight compared with ponderal index, the authors hypothesized that the fetal growth degree could be superior to the fetal growth mode and that maternal constitutional factors such as genetic growth potential could be more important than fetal nutritional deprivation to indicate long-term maternal health. This hypothesis appears in accordance with “the thrifty genotype hypothesis.”³²

Birth weight predicts maternal CVD risk,^{24,29,31} as does gestational length (see the section “Preterm delivery”). The coincidence of restricted fetal growth and prematurity shows an additive effect, yielding a more than threefold increased CVD risk.²⁹

Conflicting results are reported in literature about the association between large birth weight (macrosomia) and maternal CVD risk, recognizing both a decreased and a higher risk.^{24,25,28,29,31,33} However, given the strong associations of macrosomia with GDM and later type 2 DM,^{31,34} the presence and magnitude of the association of large birth weight with future CVD risk may depend on the population prevalence of GDM and chronic DM during pregnancy. Indeed, the association of macrosomia with CVD risk is attenuated by adjustment for GDM,²⁹ indicating that a substantial portion of the association of macrosomia and CVD is explained by underlying maternal metabolic risk.

Similarly, the association of low birth weight with maternal CVD risk may be driven by endothelial dysfunction and other pathologies associated with restricted fetal growth and preterm birth.³

Preterm delivery

PTD (<37 weeks of gestation) accounts for 6%–12% of deliveries in the developed world.³⁵ The HRs for CVD associated with total PTD are on the order of 1.3–2.6 as compared with term births.^{3,28–31,36–42} However, different values of relative risk (RR) are reported when considering the distinct phenotypes of PTD, that is, spontaneous (spontaneous labor, preterm premature rupture of membranes) or iatrogenic (medically induced labor, cesarean section). Spontaneous preterm birth is generally associated with uteroplacental inflammation, ischemia, and hemorrhage.⁴³ Further, women with a history of spontaneous PTD show higher inflammatory levels, larger waist circumference, and dyslipidemia years after delivery.²⁷ In turn, the main reasons for the medically indicated preterm deliveries include preeclampsia and fetal growth restriction, well-known risk factors for subsequent maternal CVD development. Consequently, hypertensive preterm deliveries show a stronger association with maternal CVD outcomes as compared with normotensive preterm deliveries, though the latter are still associated with a 1.2–3-fold increased risk compared with term deliveries.^{36,40,44,45} This can be likely related to the presence of common antecedents in preterm birth and CVD.^{45,46} As mentioned earlier, the possible causes of spontaneous preterm birth include infection and inflammation involving pro-inflammatory cytokines, the prostaglandin cascade, and matrix metalloproteinases.⁴⁷ The process of atherosclerosis is also largely inflammatory in its origin. Further, biochemical markers of inflammation are related to the risk of plaque rupture and endothelial dysfunction and, subsequently, to the CVD risk but also to the risk of preterm birth.^{48,49} In addition, thrombin activation by vascular lesions can be detected in the placentas of spontaneous preterm deliveries. It has been reported to be a key component in the atherosclerotic process.^{50,51}

A 39% higher risk in women delivering moderately preterm infants and a more than doubled risk in women delivering very (28–32 weeks) and extremely (<28 weeks) preterm infants has been reported, as compared with women who had a first term delivery, even after adjustment for potential confounders, including preeclampsia and smoking.²⁹ The impact of the severity of PTD on the risk of specific cardiovascular events (hypertension, ischemic heart disease, thromboembolism) and type 2 DM in the mother has also been investigated in a registry-based retrospective cohort study conducted by Lykke et al.³⁹ Included in the analysis were 782,287 women with a first delivery. After adjustments for maternal age, year of delivery, hypertensive pregnancy disorders, fetal growth deviation, placental abruption, and stillbirth, the authors identified that women delivering between 32 and 36 weeks of gestation were at higher risk for all the cardiovascular events analyzed, as compared with term controls. Further, the adjusted risk of subsequent type 2 DM increased 1.89-fold.

Hypertensive disorders

Hypertensive disorders of pregnancy are common obstetric complications that presage CVD. Preeclampsia affects approximately 2%–5% of pregnancies,^{52,53} and it still represents a major cause of perinatal morbidity and mortality.⁵⁴ In turn, incidence of gestational hypertension varies from 3% to 14%.^{52,53,55}

Although a link between preeclampsia and future chronic hypertension has already been suggested almost 50 years ago,⁵⁶ it was only recently that preeclampsia has been accepted to predispose also to premature CVD.⁵⁷

Case-control and cohort studies consistently reported that preeclampsia is predictive of future CVD and cerebrovascular disease. This risk has been summarized in two systematic reviews of controlled studies that evaluated the risk of late cardiovascular events in women with and without a history of preeclampsia.^{58,59} Compared with women with no history of the disease, preeclamptic patients were at increased risk of developing hypertension (RR 3.70; 95% CI, 2.70–5.05 at mean follow-up of 14 years), ischemic heart disease (RR 2.16; 95% CI, 1.86–2.52 at mean follow-up of 11.7 years), stroke (RR 1.81; 95% CI, 1.45–2.27 at mean follow-up of 10.4 years), and venous thromboembolism (RR 1.79; 95% CI, 1.37–2.33 at mean follow-up of 4.7 years). The absolute risk that a woman with or without a history of preeclampsia would develop one of these cardiovascular events at age 50–59 years was estimated to be 17.8% and 8.3%, respectively.⁵⁹ In addition, a graded relationship was observed between severity of preeclampsia and risk of future cardiac disease (mild preeclampsia [RR 2.00; 95% CI, 1.83–2.19], moderate preeclampsia [RR 2.99; 95% CI, 2.51–3.58], severe preeclampsia [RR 5.36; 95% CI, 3.96–7.27]), as well as correlation between preeclampsia and future peripheral artery disease (RR 1.87; 95% CI, 1.94–3.73).⁵⁸

Similar findings have been reported by prospective cohort studies published afterward.^{52,60–62} Further, the Child Health and Development Study in California, providing the longest follow-up (37 years), has confirmed that women with a history of preeclampsia in any pregnancy have a twofold increase in the risk of CVD death (adjusted HR 2.14; 95% CI, 1.29–3.57).

Women with early-onset/severe preeclampsia and PTD are at the highest risk of CVD later in life, including during the premenopausal period (Table 47.1).³⁶ In two large studies, these women had an eight- to ninefold increased risk of death from cardiovascular causes compared with women without a history of preeclampsia.^{36,62} In contrast, mild preeclampsia occurring late in gestation does not appear to be associated with a high risk of remote CVD.⁶³ The stronger association between CVD and preterm preeclampsia suggests that the pathogenesis of early versus late preeclampsia may be different.

Endothelial dysfunction is a hallmark of preeclampsia. Several studies have demonstrated that women with a history of preeclampsia or severe early-onset fetal growth restriction exhibit impaired endothelial function and peripheral vasodilation remote from pregnancy, thus suggesting that

Table 47.1 Deaths from cardiovascular causes

Population	Relative hazard rate (95% CI)
Nonpreeclamptic, term delivery	1
Nonpreeclamptic, preterm delivery	2.95 (2.12–4.11)
Preeclamptic, term delivery	1.65 (1.01–2.70)
Preeclamptic, preterm delivery	8.12 (4.31–15.33)

Source: Adapted from Irgens, H.U. et al., *Br. Med. J.*, 323, 1213, 2001.

persistence of endothelial dysfunction postpartum may contribute to the increased CVD risk identified in this patient population.^{64–67} Mangos et al. tested, 2–12 years after delivery, women who have had preeclampsia or gestational hypertension during their pregnancy, in order to investigate endothelial dysfunction, sympathetic (over)activity and/or renin–angiotensin system activation, and abnormalities of renal function.⁶⁸ Women with previous hypertensive disorders of pregnancy showed a greater BMI, more insulin resistance, and a higher awake and sleep blood pressure values, as compared with patients who have had normal pregnancies. However, none of the physiological stress tests of the sympathetic nervous system and endothelial function differed among the groups, as well as the renal function analysis. In contrast, others have reported a reduced peripheral vasodilation in women with a history of preeclampsia, when using different methods of evaluation.^{64–66,69–72}

Preeclampsia and CVD share many risk conditions such as systemic and endothelial inflammation, insulin resistance, DM, obesity, and preexistent hypertension. Elevated fasting insulin and glucose levels have been demonstrated during glucose tolerance tests in women with preeclampsia.⁷³ Also, women with a history of preeclampsia have higher serum concentrations of fasting lipids, insulin, and coagulation factors postpartum than do controls matched for BMI.^{74–76} Data from some epidemiological studies suggest that the increased risk of late cardiovascular morbidity in previously preeclamptic women reflects an underlying predisposition in these women for both disorders (genetic factors, shared risk factors), but it is also possible that preeclampsia results in permanent arterial changes leading to late CVD.^{77–80} Some investigators have hypothesized that increased insulin resistance, sympathetic overactivity, pro-inflammatory status, endothelial dysfunction, and the abnormal lipid profile in preeclamptic women constitute an early manifestation of the metabolic syndrome and that these changes persist after pregnancy, thereby putting affected women at increased risk of CVD.^{81–85} One group estimated that lifestyle interventions after preeclampsia would decrease CVD risk by 4%–13%.⁸⁶ However, it is still incompletely clarified whether preeclampsia itself, underlying risk conditions, or a combination of both contributes to future hypertension and CVD.⁸⁷

In a population-based retrospective cohort study including over one million women, preeclampsia or gestational

hypertension in the absence of GDM were associated with a twofold increase in the incidence of type 2 DM during 16.5 years of postdelivery follow-up, after controlling for several confounding variables. Unfortunately, analysis was not adjusted for prepregnancy BMI and obesity, well-known risk factors for type 2 DM development.⁸⁸ In women who had preeclampsia or gestational hypertension and GDM, the risk of future type 2 DM resulted to have a 16–18-fold increase, which is above the already elevated 13-fold increase in risk associated with GDM alone. These findings and those from previous reports^{89–91} suggest that clinicians should inform women with a history of preeclampsia or gestational hypertension that they may be at increased risk of developing DM and, likely, cardio- or cerebrovascular events. However, the available evidence did not have supported changes in standard screening guidelines so far.

Finally, since the severity of the hypertensive disorders seems to predispose to thromboembolic events,⁵⁹ caution is mandatory when prescribing oral contraceptives for these women.⁹²

Gestational diabetes mellitus

Pregnancy is characterized by progressive insulin resistance from midgestation onward. The severe insulin resistance of late pregnancy can be looked upon as a physiological test of beta-cell compensatory capacity. An optimal response to this test would be the maintenance of normal glucose tolerance in pregnancy. In turn, any abnormality of antepartum glucose homeostasis can be inferred to reflect some degree of underlying beta-cell dysfunction, with GDM representing the most severe case thereof.⁹³ Beta-cell function has been shown to progressively decrease, as glucose tolerance status worsens from normal to hyperglycemia to GDM.⁹⁴ The long-term significance of this observation is underscored by the central role of beta-cell dysfunction in the pathogenesis of type 2 DM.⁹⁵

GDM, defined as glucose intolerance that is first recognized during pregnancy, confers a fourfold to sevenfold greater risk of the incidence of type 2 DM.^{34,96,97} A population-based study reported that the incidence of type 2 DM in women with previous GDM is 3.7% 9 months postpartum, 4.9% 15 months postpartum, 13.1% 5 years postpartum, and 18.9% 9 years postpartum (versus 2% in controls without previous GDM).⁹⁸ It has been estimated that 3%–70% of women with a history of GDM will develop type 2 DM within three decades of the pregnancy.^{99,100} Waist circumference and BMI are the strongest anthropometric measures associated with the development of type 2 DM in women with GDM, as they are in women without GDM.^{98,101} Indeed, type 2 DM has been shown to develop in 50%–70% of obese women with a history of GDM, versus fewer than 25% of women with GDM who achieve normal body weight after delivery.^{102–105} Other major risk factors include gestational requirement for insulin and early gestational age at time of diagnosis.¹⁰¹

In addition to type 2 DM, this patient population is at increased risk of several other cardiometabolic abnormalities, including obesity, hypertension, and dyslipidemia.^{106–111} Given this constellation of traditional cardiovascular risk factors, it is not surprising that women with a history of

previous GDM exhibit high rates of the metabolic syndrome in the first decade following the index pregnancy.^{106,110,111} Further, these women have been linked to a variety of non-traditional cardiometabolic risk factors including increased insulin resistance, low circulating levels of adiponectin, and upregulation of inflammatory proteins.¹¹² Moreover, these patients display evidence of vascular dysfunction, including increased vessel stiffness, and impaired cardiac autonomic function.^{113–116} Finally, they have been shown to be at risk for the early onset of subclinical atherosclerosis, as indicated by increased carotid artery intima-media thickness (IMT) (the CARDIA Study—NCT00005130).⁸⁷ The carotid artery IMT has been shown to strongly predict heart disease and stroke, particularly in women. Therefore, on the basis of all of these findings, it has long been suspected that the diagnosis of GDM likely identifies a population of young women at increased risk of CVD, in addition to type 2 DM.^{117,118}

Studies have reported a 66%–85% higher risk of CVD, including coronary artery disease, myocardial infarction, and/or stroke.^{99,109,119–121} Results of the aforementioned CARDIA study demonstrated that a history of GDM signifies increased CVD risk apart from greater prepregnancy obesity, race, parity, and age. Weight gain, insulin resistance, and blood pressure partially accounted for the GDM-IMT association, thus leading the authors to suggest that body size, blood pressure control, and insulin resistance could be important modifiable risk factors that may influence progression of atherosclerosis during the midlife in women with a history of GDM. Two cohort studies reported a RR of CVD of 1.71 (95% CI 1.08–2.69, with a median follow-up of 12 years)⁹⁹ and 1.58 (95% CI 1.00–2.49, with a median follow-up of 30 years).¹⁰⁹ However, it is still unclear whether a history of GDM increases CVD risk independent of subsequent metabolic disorders, mostly due to the lack of biochemical screening for metabolic diseases before and after pregnancy in the previous studies.¹²²

Not only GDM but also lesser degrees of antepartum hyperglycemia have been associated with an elevated risk of subsequent type 2 DM and CVD.^{93,120,123–125} These data suggest that further study of the potential relationship between mild glucose intolerance in pregnancy and vascular disease is needed, as it is possible that current antepartum GDM screening may provide unrecognized insight into the future cardiovascular risk potential in young women.¹¹²

Since the maternal cardiovascular risk is associated with GDM development, the ACOG,¹²⁶ the American Diabetes Association (ADA),¹²⁷ and the Fifth International Workshop Conference on Gestational Diabetes¹²⁸ have recommended long-term follow-up of these patients. All of them need to undergo an oral glucose tolerance test 6–12 weeks after delivery, using a 2-hour 75 g oral glucose tolerance test. In case of a negative result, women should be counseled regarding their risk of developing GDM in subsequent pregnancies and type 2 DM and CVD in the future. Since lifestyle interventions, such as weight loss and exercise, are clearly beneficial for reducing the incidence of these disorders,^{129,130} they should be always performed by clinicians.

Recently, a significant correlation between GDM and long-term renal morbidity has been also reported.¹³¹ In a

population-based interventional study including deliveries occurred during a 25-year period with a mean follow-up duration of 11.2 years, the authors recognized higher rates of total renal morbidity in women with previous GDM (OR 2.3, 95% CI 1.4–3.7; $p < 0.001$) and a linear correlation between the number of GDM episodes and the risk for future renal morbidity.

Altogether these data further emphasize the importance of GDM screening to maternal future morbidity risk assessment and may initiate the discussion regarding the introduction of specific screening programs after GDM pregnancies in order to early detect vascular, metabolic, and renal diseases, thus using the benefits of secondary prevention.

First-trimester bleeding and miscarriage

First-trimester bleeding is common in pregnancy, with an incidence up to 20%–27%, and for about half of these women, the pregnancy will end in miscarriage.^{132,133} In these patients, a higher risk of ischemic heart disease later in life has already been reported.^{38,134} In turn, for women with an ongoing pregnancy, evidence has mounted in the last few years for an increased risk of later pregnancy complications such as PTD, placental abruption, and preeclampsia.^{135,136} As reported herein, these obstetric complications, as well as fetal growth restriction, are associated with increased maternal mortality and cardiovascular morbidity.

Lykke et al. conducted a registry-based cohort study, aiming to investigate the association of first-trimester bleeding without miscarriage with both prepregnancy cardiovascular morbidity and maternal long-term cardiovascular outcome.¹³⁷ The results showed that women with prepregnancy CVD were at increased risk of first-trimester bleeding and, *vice versa*, that women experiencing first-trimester bleeding were at higher risk of subsequent CVD (Table 47.2). The latter association persisted after adjustment for later pregnancy complications, which are associated with both first-trimester bleeding¹³⁶ and subsequent maternal cardiovascular morbidity,^{31,38,39,89} and thus being potential confounders. According to the intrinsic model of early vaginal bleeding, impaired cytotrophoblast invasion and spiral artery remodeling may underlie this obstetric complication. Interestingly, an altered placentation also explains the observed link to later adverse pregnancy outcomes,^{4,15,135,138} thus indicating the potential existence of a common etiology to first-trimester bleeding, adverse pregnancy outcomes, and subsequent CVD.

Recurrent pregnancy complications and maternal CVD risk

There is evidence that recurrent preeclampsia⁸⁹ and PTD^{39,40} are associated with a greater risk of CVD than a single complicated pregnancy in multiparous women. Specifically, Lykke et al. demonstrated that PTD is associated with subsequent overt type 2 DM and that the recurrence of PTD causes a twofold increase in this risk.³⁹

One-third to two-thirds of women with GDM in their first pregnancy will have GDM in a subsequent pregnancy.^{139–142} In a study including over 65,000 pregnancies, the risk of GDM

Table 47.2 First-trimester bleeding without miscarriage and subsequent maternal cardiovascular morbidity

Long-term outcome	Controls <i>n</i> = 763,976		Cases <i>n</i> = 18,311		Adjusted ^a		
	<i>n</i>	%	<i>n</i>	%	HR	95% CI	<i>P</i>
Hypertension	18,101	2.4	450	2.5	1.20	1.09–1.32	<0.001
Ischemic heart disease	8,264	1.1	252	1.4	1.58	1.39–1.79	<0.001
Stroke	8,738	1.1	249	1.4	1.41	1.25–1.60	<0.001
Thromboembolic event	3,760	0.5	121	0.7	1.61	1.34–1.93	<0.001
Diabetes mellitus	6,520	0.9	200	1.1	1.51	1.31–1.74	<0.001

^a Adjusted for the preterm delivery, primary rupture of membranes, hypertensive disorders, small for gestational age/large for gestational age, placental abruption, and stillbirth.

in the second pregnancy among women with and without previous GDM was 41% and 4%, respectively.¹³⁹ Although the association of recurrent GDM with CVD risk has not been studied, after a first GDM pregnancy, each subsequent GDM pregnancy has been associated with a modestly increased risk of type 2 DM (adjusted HR = 1.16; 95% CI, 1.01–1.34) and, likely, of cardio- or cerebrovascular events later in life.¹⁴³

Additionally, having preeclampsia,¹⁴⁴ PTD,⁴⁴ or GDM¹⁴³ in the last pregnancy appears to be associated with higher risk of future CVD in multiparous mothers, thus suggesting that pregnancy complications severe enough to contraindicate or discourage a subsequent pregnancy may be particularly potent predictors of future CVD risk.³

Non-CVD risk

Breast cancer risk

Parity

While high parity has shown a protective effect for hormone-receptor positive breast cancers,¹⁴⁵ an increased risk of estrogen receptor (ER)- and progesterone receptor (PR)-negative (ER-PR-) tumors, known to be associated with poorer prognosis compared with other cancer subtypes, has been identified.¹⁴⁶ However, emerging evidence suggests that breastfeeding may reduce this risk.¹⁴⁶ Using cases and controls taken from the Breast Cancer Family Registry, Work et al. examined reproductive risk factors in relation to ER and PR status of breast cancers. High parity (≥ 3 live births) without breastfeeding was identified as positively associated with ER-PR-tumors (OR 1.57; 95% CI, 1.10–2.24). In turn, no association with parity was found in women who breastfed for a total duration of ≥ 12 months (OR 0.93; 95% CI, 0.71–1.22).¹⁴⁷ Hypothesized potential protective mechanisms include the removal of estrogens via breast fluid, excretion of carcinogenic agents through breast milk, delay in ovulation associated with breastfeeding, and induction of terminal differentiation of breast epithelial cells.¹⁴⁸

Birth weight

Offspring birth weight has been positively associated with risk of breast cancer.^{24,28,149} Intriguingly, any increased breast cancer risk associated with bearing large infants seems to be explained

by their large, healthy placentas,^{150,151} thus hypothesizing that endocrine, angiogenic, and thrombotic processes might explain the links between offspring size and breast cancer risk.³

Preterm delivery

Several studies have reported that PTD, especially in a first pregnancy, is associated with an increased risk of future breast cancer^{36,152–155} and, perhaps, ovarian cancer.¹⁵⁶ However, data in literature are still controversial on this topic.^{151,157,158}

Hypertensive disorders

No significant association between hypertensive disorders of pregnancy and later development of cancer has been identified.^{59,159} Observational studies from the United State, Sweden, and Norway reported that women with preeclampsia were at reduced risk or had no excess risk of cancer when followed 13–19 years postpartum.^{36,150,154,157,160–162} Further, in the registry-based retrospective cohort study of Lykke et al., women experiencing hypertensive disorders of pregnancy were not identified to be at increased risk of subsequent death from noncardiovascular causes in general. Interestingly, mild preeclampsia was associated with a slightly reduced risk of death from this kind of causes.¹⁶³ In turn, a study from Israel reported an increased risk of cancer in such women (HR 1.27; 95% CI, 1.03–1.57) with a median follow-up of 29 years.^{164,165} The discordant results may be explained by several factors, including differences in patient populations, the absence of or insufficient adjustment for confounders, differences in length of follow-up, and incomplete ascertainment.

Gestational diabetes mellitus

Although a handful of studies have indicated links between type 2 DM and breast cancer,^{166,167} only a few studies have investigated whether GDM increases the risk of cancer. Thus far, reports include increased,^{166,168} decreased,¹⁶⁹ and null associations of GDM with breast cancer risk.¹⁵⁸

Renal cancer risk

Clinical and experimental findings suggest that female hormonal and reproductive factors could influence kidney cancer

Table 47.3 Combinations of preterm delivery, small for gestational age, and preeclampsia and the risk of subsequent death from cardiovascular causes

Pregnancy outcomes	All women		Death from cardiovascular causes				
	<i>n</i>	%	<i>n</i>	%	HR	95% CI	<i>P</i>
None	643,935	82.3	824	0.1	1.00	Reference	<0.001
PTD	31,132	4.0	70	0.2	1.90	1.49–2.43	<0.001
SGA	33,311	4.3	136	0.4	2.51	2.10–3.01	<0.001
PTD + SGA	5,206	0.7	27	0.5	3.30	2.25–4.84	<0.001
Preeclampsia	25,184	3.2	72	0.3	2.08	1.63–2.64	<0.001
Preeclampsia + PTD	2,662	0.3	6	0.2	2.41	1.08–5.37	<0.001
Preeclampsia + SGA	2,374	0.3	17	0.7	4.67	2.89–7.55	<0.001
Preeclampsia + PTD + SGA	2,218	0.3	10	0.5	3.85	2.07–7.19	<0.001
Missing values	36,265	4.6	148	0.4	1.25	1.04–1.50	<0.001

Source: Reproduced from Lykke, J.A. et al., *Paediatr. Perinat. Epidemiol.*, 24, 323, 2010. With permission.
Abbreviations: PTD, preterm delivery; SGA, small-for-gestational-age offspring.

development.¹⁷⁰ Interestingly, it has been reported that anatomical changes to the kidney during pregnancy might make nephrons more vulnerable to inflammation and oxidative stress.¹⁷¹

Since most studies examining the association of female hormonal and reproductive factors with kidney cancer risk have been based on small case numbers, with limited statistical power, Karami et al. decided to conduct analyses in two large, prospective cohort studies to more comprehensively investigate this association.¹⁷² No clear evidence of an association with parity and number of live births was found.

Combined pregnancy complications

Recently, Lykke et al. have reported the results of a registry-based retrospective cohort study of 782,287 women, aiming to elucidate the impact of PTD, delivery of an SGA offspring, hypertensive disorders of pregnancy, placental abruption, and stillbirth in a first delivery on subsequent rates of death from cardiovascular and noncardiovascular causes.¹⁶³

The cardiovascular mortality was increased in women delivering preterm (HR 1.90; CI 95%, 1.49–2.43), having an SGA newborn (HR 2.51; CI 95%, 2.10–3.01) or having preeclampsia only (HR 2.08; CI 95%, 1.63–2.64). A significant additive effect was identified when experiencing combinations of these (Table 47.3). In turn, only PTD of an SGA newborn related to an increased risk of death from noncardiovascular causes (HR 2.12; CI 95%, 1.72–2.62).

An interaction between gestational age and fetal growth with respect to mothers' CVD risk has also been reported by Bonamy et al. in their nationwide registry-based study. Accounting for the possible influence of maternal characteristics (e.g., smoking) and pregnancy complications (e.g., hypertensive diseases), factors associated with fetal growth restriction, preterm birth, and mother's long-term risks of CVD,^{36,45,173,174} the authors identified a significant multiplicative interaction between gestational age and birth weight standardized for gestational age. In each stratum of standardized birth weight, incidence rates of CVD increased

with decreasing gestational age. Within each stratum of gestational age, mothers to very-small-for-gestational-age infants consistently had higher risks of CVD than mothers to non-SGA or moderately SGA infants, who appeared to have similar risks. Compared with women giving birth to a non-SGA infant at term, women giving birth to a very-small-for-gestational-age infant very preterm had a tripled risk for CVD during follow-up. Further, HRs for CVD remained essentially unchanged after additional adjustment for pre-pregnancy BMI.

Physiological mechanisms linking pregnancy complications to maternal CVD risk

Pathways that link pregnancy complications to later-life CVD are still incompletely defined. Considerable evidence supports the existence of common predisposing factors for both pregnancy complications and CVD risk. However, almost no studies have investigated the alternative that pregnancy complications might cause increased CVD risk. Rich-Edwards and coworkers have analyzed evidence comparing CVD risk before, during, and after pregnancies with and without complications, trying to address this issue.³ The authors conclude that the associations of pregnancy complications with future CVD events in women are explained only in part by their associations with classic CVD risk factors of hypertension, dyslipidemia, type 2 DM, inflammation, and thrombosis, which are evident before, during, and after such complicated pregnancies.

Conclusion

The reproductive health of women provides glimpses into subclinical processes and their future risk of chronic disease. Specifically, the pregnancy complications may serve

as an early indication that a woman is on a high CVD risk trajectory, before the classic CVD risk factors (hypertension, dyslipidemia, type 2 DM, and endothelial dysfunction) are clinically detected. However, whether pregnancy complications are either mere markers of a woman's subsequent disease susceptibility, or important modifiers of pathological processes, e.g., via accelerated systemic atherosclerosis leading to cardiovascular morbidity,¹⁷⁵ is still incompletely clarified. In some cases, pregnancy complications are preceded by manifestations of the metabolic syndrome, which will predispose to later CVD.^{77,176,177} Further, a possible relationship between the individual's genotype, pregnancy complications, and subsequent CVD and death has yet to be discovered.¹⁷⁸

Further work to elucidate the endocrine, metabolic, vascular, immune, and inflammatory factors shared by reproductive disorders and chronic disease is needed. Indeed, many of the reproductive disorders overlap in definition or etiology, as in the predominance of preterm infants among the low birth weight.

Because of the progressive increase in maternal age at the first pregnancy and in the use of assisted reproduction, and the recent advances in obstetric care, the number of women having a history of pregnancy complications will continue to rise. Pregnancy may be viewed as a cardiovascular stress test, and a preterm and/or SGA delivery might be the first sign of CVD susceptibility in a woman.^{46,179}

Information about reproductive health might be used as a form of "personalized medicine" to tailor health advice to women, from early in their lives, in order to change disease trajectories before they emerge as chronic disease at menopause. The use of pregnancy complication history to screen women for targeted CVD prevention has potential to improve

public health, given the magnitude of the associations, the prevalence of the pregnancy complications, and the importance of CVD in women. Further, pregnancy complications occur early enough in a woman's life course to offer a significant preventive intervention by lifestyle changes and drug administration (i.e., statins and antihypertensive drugs). Accordingly to what reported herein, histories of preeclampsia and GDM have been recently included as part of CVD risk assessment by both the American Heart Association and the European Society of Cardiology.^{180,181}

Summary points

- Women with a history of adverse pregnancy outcome appear to be at increased risk of metabolic and vascular diseases in later life.
- Pregnancy complications and CVD and cerebrovascular diseases may have common pathogenic mechanisms.
- Pregnancy may be viewed as a cardiovascular stress test, and having a severe pregnancy complication might be the first sign of CVD susceptibility in a woman.
- Women with a history of GDM should be screened for type 2 DM and be given counseling and appropriate lifestyle advice.
- Women who have had a very-low-birth-weight baby or combined complications seem to be at severalfold increased risk of mortality from cardiovascular causes and should be screened for vascular risk factors.
- Since the severity of the hypertensive disorders seems to predispose to thromboembolic events, caution is mandatory when prescribing oral contraceptives for these women.

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48 Diabetes, pregnancy, and the developmental origins of health and disease

Gerard H.A. Visser and Mark A. Hanson

Introduction

Multiple fields of inquiry support the “developmental origins of health and disease” (DOHaD) concept, which suggests that the risk of developing some chronic, non-communicable diseases (NCDs) in adulthood is influenced not only by genetic and adult lifestyle factors but also by environmental factors acting in early life.¹ Thus, the risk of disease as an adult depends on a range of influences acting across the life course, starting with preconceptional attributes of the parents, such as nutrition and health behaviors, the intrauterine environment, birth phenotype, and aspects of the postnatal environment. These factors do not *initiate* disease in the developing embryo, fetus, or infant but have substantial influence on the ways in which the individual will respond to the challenges of their later lifestyle. Research in a range of species has shown that signals such as maternal nutritional state, stress levels, or body composition “prime” her offspring to respond to challenges such as living in an obesogenic environment.² Thus, the emerging epidemic of obesity with its resulting effects on risk of adult diabetes and metabolic abnormalities, cardiovascular disease, and some forms of cancer is not only due to the adoption of a Western lifestyle but also in part due to the intrauterine environment and other environmental factors early in life.

The rise in the prevalence of NCDs with changes in lifestyle in high-income countries is well documented. Of perhaps greater concern is the faster rise in low- to middle-income countries, especially those undergoing economic transition, with higher numbers of the population living in urban settings, the availability of fast foods of poor nutritional quality, and adoption of more sedentary lifestyle. In addition, global improvements in public health have reduced mortality in early life and increased longevity, leading to greater incidence of chronic disease. The concept of “mismatch”³ explains how the transition from a poor to a rich lifestyle within a generation leads to a greater risk of

disease such as diabetes in the offspring. However, it is now recognized that diabetes can also be passed from one generation to a subsequent generation, or even to more than one generation.⁴ Thus, for example, populations in which the prevalence of diabetes has increased following economic improvements leading to mismatch now suffer greater incidence in subsequent generations as “diabetes begets diabetes.”

In this chapter, the impact of pregnancy in women with preexisting or gestational diabetes mellitus (GDM) on the long-term outcome of their offspring is discussed, in the context of the altered intrauterine environment, with maternal obesity as an increasing comorbidity. Prevention of excessive fetal growth is likely to be an important preventive measure to prevent long-term morbidity in these offspring. Early diagnosis of those at risk will be crucial if interventions are to be instituted in good time.

Diabetes in pregnancy and long-term outcome on offspring

Animal studies

First data on the effects of altered intrauterine glucose homeostasis on the next generation came from studies in rats. Mild diabetes during pregnancy induced by streptozotocin resulted in impaired glucose tolerance and GDM in offspring; the effects on glucose tolerance extended to the third generation.⁵ A large number of studies followed in many species, showing that such effects on glucose/insulin homeostasis could also be produced by unbalanced maternal nutrition (over- or undernutrition) by administration of glucocorticoids or exposure to endocrine disruptor chemicals in pregnancy.^{6–8} The processes by which these effects occur have been shown to involve developmental plasticity, in particular epigenetic effects that permit multiple phenotypes to be induced from a genotype, dependent on the developmental environment.⁹

Most recently, such effects on the offspring of several generations have also been shown to operate via the paternal line.^{10,11}

A set of identified, independent risk factors impacting outcome in offspring of women with diabetes is shown in the following:

- Genetic predisposition
- (Gestational) diabetes
- Maternal body mass index (BMI)
- Weight gain in pregnancy
- Macrosomia at birth
- Cesarean delivery (CD)
- Excessive weight gain >2 years of age
- Socioeconomic circumstances

Maternal diabetes and diabetes in offspring

The impact of hyperglycemia during fetal development on the offspring has been studied in Pima Indians in the United States, a population poorly adapted for Westernized diets and sedentary lifestyles common today, and thus with a high propensity toward the development of diabetes. In Pima Indian women, non-insulin-dependent diabetes mellitus (NIDDM) during pregnancy results in offspring who, at ages 20–24, themselves have a much higher prevalence of NIDDM (45%) than do the offspring of nondiabetic Pima Indian women (1.4%) or the offspring of Pima Indian mothers who developed diabetes after the pregnancy (8.6%).¹² These differences remained statistically significant after taking into account paternal diabetes, age at onset of diabetes in the parents, and the offspring's weight relative to height. Thus, in this diabetes-prone population, there is a dramatic increase in the development of diabetes among those offspring who gestated in an abnormal intrauterine environment defined by diabetes-driven hyperglycemia. In contrast, in Europe, women with either GDM (compared with pregnant women at genetic high risk for, but without, GDM) or type 1 diabetes (compared to the general population) tended to have offspring that are approximately 8% more likely to develop T2D or impaired glucose tolerance by the age of 27¹³; in this European population less prone to develop diabetes, the effects of intrauterine hyperglycemia are less pronounced but still detectable. It, therefore, appears that both genetic and epigenetic predispositions may differ between populations and play a role in determining risk of adult diabetes. Unfortunately, maternal BMI was not taken into account in these studies.

Maternal BMI and obesity in offspring

GDM in the mother is associated with a range of effects on the offspring.^{14,15} Fetuses of women with GDM develop insulin resistance in utero, but mainly in the case of maternal obesity. In fact, data suggest that obesity is the more important factor impacting long-term weight outcomes for offspring, not GDM. A recent Finnish study demonstrated that overweight and abdominal obesity in

16-year-old adolescents was related to maternal obesity, and especially to the combination of maternal obesity and GDM, but *not* to GDM alone.¹⁶ A meta-analysis has suggested that there is an association between all types of diabetes in pregnancy and childhood obesity; however, only three studies in the meta-analysis corrected for maternal BMI, and in all three of those studies, the direct relationship between maternal diabetes and childhood obesity was lost following correction for BMI.¹⁷ Similarly, a study of metabolic syndrome in infants at the age of 7–11 years has shown that maternal obesity or being large for gestational age at birth were independently associated with metabolic syndrome but not maternal GDM.¹⁸ In a recent review by Donovan and Cundy,¹⁹ it was concluded that exposure to hyperglycemia in utero has minimal direct effects on the later risk of obesity and type 2 diabetes. The increased risk of obesity in the offspring of women with type 2 diabetes or GDM can be explained by confounding factors, such as parental obesity. In women with type 1 diabetes, it has been shown that childhood obesity at the age of 7 and increased insulin resistance were independently related to maternal BMI and being large for gestational age at delivery.²⁰ Thus, there is doubt as to the independent impact of maternal preexisting diabetes or GDM on obesity in the offspring, although data corrected for maternal BMI are limited. The effect of maternal diabetes on outcome may be related to an increased and proportionally abnormal fetal growth resulting in macrosomia at birth. The impact of maternal obesity, irrespective of the presence of diabetes or otherwise, has also been shown in a large population study in Scotland, in which an excess of premature mortality from cardiovascular events was found in adult offspring.²¹ In this study, data were adjusted for maternal age at delivery, socioeconomic status, birth weight, and gestational age at delivery. Maternal BMI was not taken into account.

Weight gain during pregnancy

An increased weight gain during pregnancy has been shown to be related to fetal macrosomia at birth in women with type 1 diabetes.²² High maternal weight gain is also associated with increased body weight in a 12-year-old offspring, and this effect appeared only partly mediated through a higher birth weight.²³ Similarly, associations have been found between gestational weight gain with offspring BMI and blood pressure at 21 years of age.²⁴

Fetal macrosomia

Being large for gestational age at birth is a risk factor for childhood obesity both in offspring of women with diabetes^{16,20} and in nondiabetic populations.¹⁶ This may be due to epigenetic changes induced by an abnormal intrauterine environment, by genetic differences (in relation to a high maternal BMI) or altered nutrition and activity pattern during childhood. The latter may be due to impaired socioeconomic circumstances and related unhealthy

lifestyle. Animal data have shown that “cafeteria style” diet during the newborn period will result in obesity and glucose intolerance during pregnancy and in glucose intolerance in the following generation.²⁵ There is evidence that the highest incidence of childhood obesity occurs in offspring of women with type 2 diabetes in whom abnormal intrauterine environment, increased maternal BMI, and suboptimal socioeconomic circumstance may come together.²⁶ In offspring of women with type 1 diabetes, type 2 diabetes, and GDM, childhood obesity is most common in infants being large for dates at birth, with the highest incidence of obesity in large-for-dates infants of obese women with type 2 diabetes (Hammoud et al., unpublished data).

Cesarean delivery

Women with diabetes deliver generally two to three times as much by cesarean section than control women. CDs result in a 20%–30% higher incidence of autoimmune disease and obesity in the offspring. This has been shown most convincingly in meta-analyses of observational studies regarding childhood diabetes and asthma.^{27,28} Although these data did not derive from randomized controlled trials, subanalysis did not reveal effects of low-birth-weight infants, breastfeeding, and passive smoking. Moreover, funnel plots did not show evidence of publication bias.²⁷ The effects of CDs on the immune response may be due to the absence of the stress of the normal labor process, resulting in maladaptive immune activation. Other possibilities include altered epigenetic regulation of gene expression and perturbed bacterial colonization of the gastrointestinal tract.²⁹ After a CD, there is a delayed and altered bacterial colonization with reduced variation.^{30,31} This may result in delayed developmental balance between TH-1 and TH-2 immune responses.³² A meta-analysis of 15 studies with a combined population of over 160,000 individuals has shown a 22% increase in obesity in children, adolescents, and adults after having been born by cesarean section.³³ The microflora in the gut may stimulate fat deposition and promote obesity through several mechanisms, by improving energy yield from food; by regulating gut permeability, low-grade inflammation, and immune balance; or by modulating metabolism and/or genes directly in the liver.³⁴ All in all, it can be concluded that microflora during early life play a significant role in health and disease.³⁵ In women with diabetes, a CD may have an effect on the incidence of type 1 diabetes and/or obesity in their offspring.

Accelerated growth in offspring >2 years of age

Finally, persuasive evidence of the impact of early childhood growth on the development of T2D has been presented by Eriksson et al. in their longitudinal archival study of 8760 subjects born in Helsinki from 1934 to 1944.³⁶ Subjects were divided into those weighing ≤ 3.5 kg at birth, and those weighing >3.5 kg at birth. In both groups of subject, rapid gain in BMI after the age of 2 years was associated with an increased risk of T2D in later life. These data suggest the

potential value in ensuring that children over the age of 2 do not grow too quickly or gain weight disproportionately to their gains in height, which may induce epigenetic changes that impair glucose tolerance and set the stage for diabetes. Similarly, accelerated growth has been found in infants of women with type 1 and type 2 diabetes.^{20,26} Concentrated public health efforts focused on adequate diet and sufficient exercise early in childhood and more study on interventions such as folic acid that may potentially minimize epigenetic insults during pregnancy³⁷ are both high priorities to help stem the ongoing epidemic of diabetes across the globe, an epidemic that threatens to become a worldwide pandemic in the years ahead, with particular burden placed on the developing world.³⁸

Discussion

The data presented in this chapter indicate that many factors may play a role in the outcome of offspring of women with diabetes. The strongest relationship with diabetes and/or obesity in offspring concerns most likely the preexisting maternal BMI and fetal macrosomia at birth. The latter is affected by maternal diabetes and concomitant abnormal intrauterine environment and maternal weight gain during pregnancy. There is evidence that macrosomia in fetuses of women with type 1 and type 2 diabetes is increasing in the Western world, despite improvements in glucose control during pregnancy.^{39–42} This unexpected finding is likely to be due to an increase in maternal BMI, reduction in maternal vascular complications, better glucose control in early pregnancy resulting in a better placentation, increase in weight gain during pregnancy, and poorer control (especially postprandially) near term since women are not admitted routinely to the hospital anymore.^{22,43,44} Reduction of macrosomia at birth seems difficult, with reducing of weight gain during pregnancy as one of the few modifiable options. Prevention of excessive growth during childhood might be a secondary tool to prevent negative long-term effects of fetal overgrowth. Achievement of normoglycemia is the most important factor but appears difficult at present. Continuous glucose measurements have shown that glucose values of women with type 1 diabetes are on average almost 2 mmol/L higher than in control pregnancies.⁴⁵ A first randomized trial on the use of a real-time continuous glucose sensor, five times during pregnancy for 4–6 days, failed to show an improved outcome in women with type-1/2 diabetes, maybe because this device facilitates enhanced food intake that may promote fetal growth.⁴⁶ However, a recent study from China has shown that continuous glucose measurements and intensive dietary counseling in women with GDM were associated with better glycemic control and a significantly lower incidence of large-for-dates newborn infants.⁴⁷ Intensified glucose monitoring in combination with regular dietary counseling may therefore be able to reduce macrosomia at birth and hopefully reduce long-term impairments.

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49 Interventions to improve pregnancy outcome in obese pregnancy: Implications for mother and child

Rahat Maitland and Lucilla Poston

The majority of adverse complications of obese pregnancies for both mother and child are strongly associated with pre-pregnancy BMI¹; therefore, it can be reasonably assumed that preconception is the optimal time to introduce strategies to encourage weight loss so that women become pregnant with a healthy BMI. However, as a large proportion of pregnancies are unplanned, this approach will only be appropriate for a motivated subgroup, until such time when public health strategies to reduce weight in adolescents and young adults have met with success. Most intervention strategies therefore focus on the pregnant woman, and in recent years, as the global epidemic of obesity has spiralled, so have the number of studies attempting to reduce the burden of obesity on the health of the mother and her child. While interventions to obese subjects often meet with failure in the general public, encouragement can be taken from the knowledge that pregnancy is often a time of high motivation for women, to address and maximize not only their own health but that of their unborn child. Given the increasing evidence that a child nurtured in utero by an obese woman may have an increased risk of obesity and cardiometabolic disease in later life,² interventions in pregnancy may also have the benefit of impacting favorably upon the health of the next generation.

Interventions to limit gestational weight gain

Intervention strategies designed to improve outcomes for mother and child in overweight and obese pregnant women have included dietary advice^{3–5} or physical activity (PA)^{6–8} or, more frequently, a combination of the two.^{9–13} To date, the outcome of choice has predominantly been gestational weight gain (GWG). Since there is a strong association between maternal prepregnancy BMI and clinical outcomes, the emphasis

on GWG may be less appropriate for obese women than for those with a lower BMI, although achievement of the Institute of Medicine (IOM) recommendation of 5–9 kg (for women with a BMI > 30 kg/m²) would inevitably reduce postpartum weight retention and thereby decrease the risk of adverse outcomes, including delivery of an large for gestational age (LGA) infant in a subsequent pregnancy.¹⁴ Recent meta-analyses have, however, identified many of these studies to be poorly designed and most to be underpowered for clinical outcomes.^{15–19} The results have generally been disappointing with very modest reductions in GWG, e.g., 2.2 kg, in one meta-analysis¹⁷ and with relatively few women achieving the IOM recommended limits of GWG. Moreover, evaluation of an intervention on the woman's diet or PA, in order to determine compliance, has not always been undertaken. Of those that have evaluated the women's diet, some have shown the desired effect, with significant changes including reduced calorie and saturated fat intake and an increase in polyunsaturated fats or improvements in fiber consumption.^{3,9,20} Less frequently, an increase in PA has been reported.^{13,21} Compliance to the intervention is important to assess, as failure to change GWG could arise either from poor compliance to the intervention or because of the lack of effectiveness. Some interventions have been underpinned with theoretical strategies designed to support behavioral change and others have not. One meta-analysis to determine the most effective intervention strategy for limiting GWG in women of all BMIs concluded that those that did not address theories of behavioral change were less effective than those that did²² but an updated systematic review suggests that either approach is equally effective.²³ These authors concluded that motivational interviewing and behavioral self-monitoring are likely to be key factors in achieving limitation of GWG, especially if coupled with dietary interventions.

The evidence for any clinical benefit of a modest limitation of GWG achieved through intervention studies in overweight and obese pregnant women is less than

encouraging, as indicated by several meta-analyses. Dodd et al. reported no significant effect on birth weight, macrosomia, cesarean section rate, gestational diabetes mellitus (GDM), or any other clinical outcome.¹⁵ More recently, Oteng-Ntim et al. reported a significant reduction in GWG of 2.21 kg in obese and overweight women with an associated lower incidence of GDM (odd ratio 0.80, [95% confidence interval [CI] 0.58–1.10]), but the strength of evidence was considered low.¹⁷ In a subgroup of obese women, part of a large meta-analysis of interventions on GWG in women of all BMIs, Thangaratnam et al. also arrived at the same conclusion.^{18,19} One of the few studies in obese pregnant women to have shown improvement of relevant biochemical outcomes was a rigorous, intensive dietary intervention in 50 obese pregnant women, designed to restrict GWG to 6–7 kg and proposing adherence to the official Danish dietary recommendations (fat 30E%, protein 15E%–20E%, and carbohydrate 50E%–55E% [E% = % of total energy]). Compared to other studies, a considerable reduction in GWG was achieved, being reduced by half (6.6 vs. 13.3 kg, [95% CI 2.6–10.8], $p = 0.002$). This was also associated with a reduction in the fasting plasma insulin concentration from 15 weeks onward. At 27 weeks gestation, a 20% reduction in plasma insulin was observed with a further 23% reduction at 36 weeks.³ The intervention, however, had no effect on the incidence of GDM, but the study was likely to have been underpowered for this outcome.

These negative data from interventions primarily targeting GWG are perhaps unsurprising as evidence suggests that prepregnancy BMI may contribute as much to adverse outcomes as excessive GWG.¹ Approaches that focus on limitation of weight gain in obese pregnant women may therefore be misplaced.

Safety considerations of limiting GWG

Thus far, no adverse effects of limiting GWG within recommended limits in obese pregnant women by dietary or exercise interventions have been reported.^{4,11,24–26} However, caution should be heeded, as observational studies have highlighted deleterious consequences for those who gain less than 5 kg (the lowest gain advised by the IOM for BMI ≥ 30 kg/m²), including adverse effects on fetal growth. The most comprehensive review to address this issue is a retrospective analysis of 1241 overweight and obese women who had participated in prospective observational studies.²⁷ Of the total sample, 15.2% ($n = 188$) gained or lost less than 5 kg and for these women, the incidence of small for gestational age (SGA) and low birth weight was significantly greater than for those whose GWG exceeded 5 kg. Their infants had significantly less total (403 $\pm$ 175 vs. 471 $\pm$ 193 g, $p < 0.0001$) and lean fat mass (2855 $\pm$ 321 vs. 2995 $\pm$ 347 g, $p < 0.0001$) with smaller head circumference (34.2 $\pm$ 1.7 vs. 34.5 $\pm$ 1.7, $p = 0.02$) and reduced length (49.3 $\pm$ 2.3 vs. 50.0 $\pm$ 2.8, $p = 0.001$), reflecting reduced skeletal growth. The risk of SGA was independent of maternal glucose status, and the exclusion of all women with GDM from secondary analysis did not alter the results.

The DALI study (ISRCTN70595832), a collaborative European randomized controlled trial (RCT) of a vitamin D and lifestyle intervention in different combinations for obese pregnant women, is currently underway and may provide more insights into the effects of restricting GWG (target sample size 880) and the safety in terms of clinical outcomes. Women in the lifestyle intervention arms (dietary, PA, or a combination of both) are advised to limit GWG to <5 kg. Primary outcomes are GWG, insulin sensitivity (homeostatic model assessment of insulin resistance [HOMA-IR]), and fasting blood glucose (FBG) measured following 75 g oral glucose tolerance test (OGTT) at 24–28 and 35–37 weeks gestation. Prenatal ultrasound scanning will enable detailed intrauterine dimensions to be made, and within 48 of birth, neonates will have full anthropometric assessment.²⁸

Intervention studies aimed to improve glucose metabolism and reduce GDM incidence

Since the increased risk of GDM is a consequence of insulin resistance (IR) and because IR underpins the majority of adverse outcomes of pregnancy in obese women, approaches that focus on IR or GDM as primary outcomes in high-risk women may be more profitable than a focus on restriction of GWG. However, despite the strong evidence to support lifestyle changes in reducing the risk of type 2 diabetes mellitus (T2DM),^{29–31} results of meta-analyses regarding interventions to reduce GDM in women of all BMIs have been contradictory, leaving many unanswered questions.^{32,33}

Physical activity

PA is an established method of improving insulin sensitivity and overall glycemic control in addition to reducing cardiovascular risk by influencing multiple clinical and biochemical variables associated with adverse events including glycated hemoglobin (HbA1c), systolic blood pressure, adiposity, and triglycerides in subjects with T2DM.³⁴ The acute effects of exercise can increase insulin-mediated uptake by the skeletal muscle by up to 40% for 16 hours, with long-term effects from sustained activity thought to be mediated via increased glucose transporter type 4 (GLUT 4) production.³⁵ In the absence of any weight loss, improvements in peripheral insulin sensitivity and activity of lipoprotein lipase, an enzyme involved in the catabolism of triglyceride-rich lipoproteins and strongly associated with IR, have been reported in sedentary adults following a 6-month walking program.³⁵ The progression to overt diabetes in high-risk individuals including those who are obese with known glucose intolerance can be limited, but the optimal mode, frequency, intensity, and duration of exercise is yet to be identified.^{29,36}

In pregnancy, among women of normal BMI, increasing PA also improves glucose tolerance.³⁷ However, advancing gestation and physical restriction coupled with maternal anxiety is often considered a barrier to exercise in pregnancy in women of all BMIs. Most exercise-only interventions center around supervised exercise classes two to three times a

week, adapted for pregnancy with a qualified trainer, with or without a home-based element.^{6,21,38–40}

While one meta-analysis showed strong inverse associations (25%–55% reduced risk) between PA before or during early pregnancy and GDM,³² a more recent report of six RCTs of PA in of a total of 1278 subjects³³ suggested that there was insufficient evidence to support the use of PA to prevent GDM (risk ratio 0.91 [95% CI 0.57–1.44], $p = 0.68$).

Following the Hyperglycemia and Adverse Pregnancy Outcomes study,⁴¹ new guidelines for the diagnosis of GDM were agreed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) advocating lower glucose thresholds than those used previously (fasting glucose ≥ 5.1 mmol/L, or 1-hour glucose ≥ 10.0 mmol/L, or 2-hour glucose ≥ 8.5 mmol/L [75 g OGTT]).⁴² In 2013 these were also endorsed by the World Health Organization.⁴³ Using these new diagnostic criteria, a recent RCT of PA and GDM in 510 healthy Spanish pregnant women of normal BMI found no reduction in GDM between exercising and nonexercising groups.²⁶ This concurs with a Norwegian study of lean women ($n = 702$) that adopted a less intense intervention.²⁵ However, neither study measured compliance to the intervention, i.e., whether PA changed in the intervention arm of the study.

There has been limited success in PA interventions in overweight and obese pregnant women. In a feasibility study, Callaway et al. reported a modest increase in PA among obese pregnant women who received an individualized exercise program, but did not consider this would be adequate to reduce GDM.²¹ The FitFor 2 program found no significant differences in maternal FBG, fasting insulin, HbA1c, BMI, or birth weight following a PA intervention (60 minutes aerobic exercise in sessions twice a week) in women at high risk of GDM (BMI ≥ 30 or >25 kg/m² plus one other risk factor).⁷ Lack of statistical power may have confounded the results; however, compliance to the sessions was poor, with only 16.3% of women attending half of the total number of sessions (two per week), and compliance decreased with progression of pregnancy. Several studies have addressed the barriers to changing PA behavior among obese pregnant women, which have included physical discomfort, concerns about safety for the baby, and social and cognitive factors.^{44,45} The high incidence of depression among obese pregnant women may also contribute to a lack of enthusiasm.⁴⁶

Pharmacological interventions

Metformin exerts its glucose-lowering effects by reducing hepatic gluconeogenesis and improving peripheral insulin sensitivity, by mechanisms that are not fully understood. The resultant reduction of blood glucose concentration without corresponding hypoglycemia or weight gain, an unwanted side effect of many other agents used for T2DM, makes it a desirable option for treatment of GDM since they both share a common metabolic pathway of IR and inflammation. Metformin crosses the placenta and therefore its use in pregnancy has until recently been limited because of concern of its potential effects on the mother and fetus.⁴⁷

The Metformin in Gestational Diabetes (MiG) trial, the largest RCT of 751 subjects comparing metformin therapy vs. insulin for women diagnosed with GDM from 20 to 33 weeks gestation (mean BMI for metformin and insulin groups 35.1 ± 8.3 kg/m² and 34.6 ± 7.2 kg/m², respectively), found no significant difference in the composite primary outcome of neonatal complications.⁴⁸ Acceptability and compliance with metformin treatment were high, and women in this group experienced less GWG and greater postpartum weight reduction at 6–8 weeks.

Metformin has also been used to induce ovulation in women with subfertility and polycystic ovary syndrome, a condition also characterized by IR, with no adverse pregnancy outcomes reported. Thus, it might appear reasonable to use metformin as an intervention in nondiabetic obese pregnant women from early pregnancy onward. Two multicenter RCTs of metformin vs. placebo with no other lifestyle or dietary restrictions are in progress. The “Metformin in Obese Nondiabetic Pregnant Women” (MOP: NCT01273584) and “Efficacy of Metformin in Pregnant Obese Women” (EMPOWaR: ISRCTN51279843) studies are recruiting women from 12 to 16 weeks gestation with slightly different entry BMI values (BMI ≥ 35 kg/m² for MOP and ≥ 30 kg/m² for EMPOWaR). Exclusion and inclusion criteria are otherwise similar but non-Caucasian women are excluded from EMPOWaR.

Theoretically, the metabolic profile of infants exposed to metformin could be favorably altered and accompanied by changes in adipose tissue distribution. This has the potential to reduce the heightened lifetime risk of cardiovascular morbidity and premature death reported in children of obese mothers.^{2,49} The MiG TOFU (the offspring follow-up study) follow-on study has, however, identified some potentially concerning differences in body composition in children at 2 years using a combination of body composition measures in a subgroup of 318 children from the MiG study.⁵⁰ Overall body fat and estimates of visceral fat measured by dual energy X-ray absorptiometry and bioimpedance studies were equivalent but children in the metformin arm had greater measures of subcutaneous fat stores at three sites: subscapular (6.3 ± 1.9 vs. 6.0 ± 1.7 mm, $p = 0.02$) and biceps skinfold (6.03 ± 1.9 vs. 5.6 ± 1.7 mm, $p = 0.04$) and mid-upper arm circumference (17.2 ± 1.5 vs. 16.7 ± 1.5 cm, $p = 0.002$). The original hypothesis that in utero metformin exposure would be associated with less visceral fat and thus less IR in the offspring was not met. Nonetheless, the authors concluded that increases in subcutaneous fat stores may be a preferential and healthier response to metformin with an ultimate reduction of visceral fat in the long term. Longer-duration follow-up studies, ideally from large RCTs such as MOP and EMPOWaR, are required.

Targeted postprandial glucose interventions and the GI

Studies from more than 20 years ago showed that postprandial glucose has a stronger association with macrosomia than FBG therefore interventions specifically aimed at reducing the postprandial glycemic response seem warranted to

improve pregnancy outcome in women who have GDM or who are obese and insulin resistant.⁵¹

Dietary advice remains the cornerstone of treatment for GDM, with increasing use of second-line therapies, particularly insulin and metformin for women who are unable to achieve adequate control with dietary changes alone.^{52,53} Two seminal RCTs have unequivocally demonstrated that treatment of mild glucose intolerance in pregnancy improves neonatal and maternal outcomes.^{54,55} In one study, the Australian Carbohydrate Intolerance Study in Pregnant Women, women with mild glucose intolerance, randomized to the intervention group, received dietary advice and only commenced insulin when fasting and/or postprandial blood glucose targets were exceeded on more than two occasions. A significant reduction in serious perinatal complications was achieved in the intervention arm, and although 20% of women in this group were commenced on insulin to optimize glucose control, it is important to highlight that the majority of women were successfully managed with dietary advice alone.⁵⁴

Low glycemic index (LGI) diet

Otto and Niklas first observed the different glycemic response to various foods in 1980 with the subsequent concept of the glycemic index (GI) food classification system developed by Jenkins in Toronto shortly thereafter.⁵⁶ Initial studies compared a 50 g portion of carbohydrate calculated from published food tables to a standard of 50 g glucose. Following consumption of the carbohydrate, serial venous blood samples were taken up to 2 hours and glucose values plotted to determine the area under the curve (AUC). Similar methods are adopted today however the use of capillary blood glucose is more frequently utilized against a standard of white bread. The AUC for each food is expressed as a percentage of the mean AUC for the standard, from a sample of 10 subjects, and used to calculate the GI.⁵⁷ The GI predicts the ranking of the glycemic response of foods in an individual; foods that are digested and absorbed slowly raise blood glucose concentrations gradually and are thus given low GI (LGI) values. The division of GI values into three simple categories has facilitated a useable system for individuals and generated an additional tool for the delivery of dietary advice for healthcare professionals; high GI ≥ 70 , medium GI 56–69, and LGI < 55 .

Inherent and important limitations of GI classification exist when applying the principles to the wider population and when interpreting individual responses to foods of different categories. Aberrations in methodology are known to affect the GI including food portion size and preparation, the choice of standard, timing of test, frequency of blood sampling, and the formula used to determine the AUC.⁵⁷ Subject characteristics such as age, sex, ethnicity, degree of glucose intolerance, and coexisting disease that may influence glucose absorption are also confounders but attempts to standardize that these factors would serve to limit the variability in glucose response and maintain consistencies across food groups tested, therefore minimizing the effect on overall GI.⁵⁸

LGI and obesity

A Cochrane review of the evidence for the use of LGI diets in obese subjects (in nonpregnant subjects) included six eligible RCTs with a total of 202 subjects. Obese and overweight subjects who followed the LGI diet had significantly greater weight loss (weighted mean difference -1.1 kg [95% CI -2.0 to -0.2]) and reductions in total cholesterol and LDL concentrations compared to subjects on standard or high-GI diets (WMD [weighted mean difference] -0.22 mmol/L, [95% CI -0.43 to -0.02] and WMD -0.24 mmol/L, [95% CI -0.44 to -0.05] for standard and high GI, respectively).⁵⁹ Subsequently, Liu et al. demonstrated a significant reduction in serum glucose and insulin AUC (42% and 29%, respectively) when comparing diets of LGI/low carbohydrate to high GI/high carbohydrate in overweight and obese people.⁶⁰

LGI diet and diabetes

A Cochrane review published in 2009 and an earlier meta-analysis both concluded that a modest, yet clinically useful, reduction in HbA1c of 0.5% can be achieved with a LGI diet in the management of diabetes, equivalent to the changes observed with single-agent pharmacotherapy.^{61,62} Similar limitations of small sample size and variation in duration of diet were reported and both reviews included participants with T1 and T2DM.

LGI and pregnancy

Two systematic reviews are inconclusive to support universal recommendation of LGI diets to prevent or treat GDM in pregnant women.^{63,64}

The Camden study, a prospective analysis of dietary GI calculated from three 24-hour recall questionnaires over the course of pregnancy, in 1082 women reported a positive and significant relationship between GI, maternal HbA1c, and plasma glucose 1 hour following 50 g glucose challenge test (GCT) at 24–28 weeks gestation.⁶⁵ Similarly, GI was positively related to fetal growth.

Louie et al. conducted a systematic review of LGI diets in pregnancy for women of all BMI categories including three studies complicated by GDM.⁶⁶ Of the eight studies included, half showed positive influence of a LGI diet on pregnancy outcomes, with a reduction in LGA reported in two but a moderate increase in the delivery of an SGA infant in one.

In general, LGI diets have been shown to be safe in pregnancy with no adverse maternal effects reported, but issues regarding restricted fetal growth have been identified.⁶⁵ These concerns have not been reproduced in subsequent studies and will continue to be addressed by ongoing larger intervention trials.

Randomized controlled trials of LGI interventions in over weight and obese pregnant women

The three largest RCTs aimed at lowering the GI of the diet, in conjunction with supporting a healthy lifestyle in high-risk pregnant women, have completed recruitment,^{12,67,68} and two

have published the outcomes.^{12,67} While the recently reported Pregnancy and Glycemic Index Outcomes study did not specifically recruit obese women (mean BMI 24.5 kg/m²) and included those with normal glucose tolerance, the results nonetheless merit mention.⁶⁹ In an RCT, LGI dietary advice was compared to routine healthy eating with both arms receiving equivalent support and contact from the research team and dietitian from 20 weeks onward. In contrast to an earlier but smaller study from the same group, no significant differences were observed for the primary outcomes of birth weight, birth centile, or ponderal index.⁷⁰ The failure to replicate the findings in the larger cohort with women of similar characteristics is perhaps unsurprising since the advice given to the control arm was a healthy diet, reinforced with dietary counseling, in contrast to standard antenatal care in the earlier study, where women were reported to consume a high GI diet reflective of habitual diet.

Low glycemic index diet in pregnancy to prevent macrosomia (ROLO study): Randomised control trial

The ROLO study hypothesized that an LGI diet would reduce recurrence of macrosomia in subsequent pregnancies for women who had previously delivered an infant >4000 g vs. standard antenatal care with no dietary advice ($n = 781$, mean BMI 26.8 kg/m²).⁷¹ No difference in the primary outcome was observed, but positive findings were noted for those following the LGI diet. At 40 weeks gestation, women in the intervention arm had gained 1.5 kg less weight than controls (mean difference -1.3 , [95% CI -2.4 to -0.2], $p = 0.01$), and fewer exceeded the 2009 IOM guidelines for GWG (38% vs. 48% for LGI and control, respectively). Both FPG and 1 hour glucose following 50 g GCTs were significantly lower in the LGI group, although the incidence of GDM following 100 g glucose load was no different.⁶⁷

Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial

LIMIT was the first adequately powered lifestyle intervention RCT for obese and overweight pregnant women with 2212 participants randomized to a combined program of dietary and exercise advice (in conjunction with behavioral strategies) or to standard antenatal care. The intervention was delivered over three visits with a research dietitian and reinforced by three additional telephone consultations with trained assistants.¹² Dietary advice was not principally centered on LGI principles but incorporated food exchanges, increased fiber and fruit consumption, and reduction of refined sugars to maintain a eucaloric diet with a global effect of lowering overall GI.⁷² The primary outcome of a reduction in LGA incidence (birth weight ≥ 90 th centile for gestational age and sex) compared to control was not met. Pregnancy outcomes including the diagnosis of GDM and GWG were the same; however, there was a reduction in the risk for the secondary outcome of macrosomia in the intervention group (15% vs. 19%, relative risk 0.83, [95% CI 0.68–0.99], $p = 0.04$).

UPBEAT (ISRCTN 89971375)

The UPBEAT (U.K. Pregnancies Better Eating and Activity Trial), which has recently completed recruitment and has yet to report outcomes, is a multicenter RCT of a complex dietary and PA intervention aimed at improving glucose homeostasis in obese pregnant women ($n = 1546$). Following randomization at 15⁺⁰–17⁺⁶ weeks gestation to intervention or standard antenatal care, the program is delivered over 8 weekly group sessions with a health trainer until OGTT at 27⁺⁰–28⁺⁶ weeks gestation. The objective of the dietary recommendation is to reduce the GI and glycemic load ($GL = GI \times \text{carbohydrates [g]/100}$) using food swaps and to exchange saturated fatty acids (SFAs) for monounsaturated and polyunsaturated fatty acids. Women maintain contact with the research team with further three structured visits until delivery where dietary data, blood samples, and anthropometry are obtained. Within 72 hours of birth, a detailed anthropometric assessment of the baby is made that is repeated at 6 months' postnatal review.

The study endpoints include maternal and neonatal primary outcomes of, respectively, GDM diagnosed by 75 g OGTT using the recommendations of the IADPSG⁴² and LGA delivery, defined as adjusted birth weight >90th centile for gestational age using customized centiles, where adjustment is made for maternal height, weight, ethnicity, parity, and infant sex.⁷³

A pilot trial for UPBEAT was undertaken in 183 women in four urban U.K. hospitals, to evaluate changes in dietary and PA behaviors in response to the intervention, to trial all aspects of the protocol, and to undertake process evaluation.⁷⁴ Baseline habitual diets for all women were similar with no differences in the following: total energy intake, GI, GL, and macronutrient composition. At 28 weeks gestation, there was a significant reduction in total energy intake, GL, total fat, and SFA with an increase in fiber consumption (nonstarch polysaccharides) for the intervention group. Women entered the study with a medium GI diet (58), but after 8 weeks of adherence to the program, a borderline significant 7-point reduction in the GI was achieved, and the diet of the intervention group was reclassified as LGI (difference -7 , [95% CI -15 to 0], $p = 0.054$). On completion of the study, analysis will determine whether these positive dietary changes are maintained throughout pregnancy and beyond and whether they translate into favorable clinical outcomes.

In summary, for all the pregnancy interventions discussed, the additional commitment over and above the time required for routine antenatal care is a limitation particularly for women in full-time employment or with childcare responsibilities. Poor compliance and high dropout rates are greatest in women from ethnic minorities and those who have not received higher education.^{7,11,21} Authors have attempted to facilitate participation by various means including local delivery, providing transport to and from research centers, and regular phone, postal, and email contact, but greater understanding of barriers to behavioral change, particularly to increased PA, is needed.

Adequately powered RCTs are required to determine whether the interventions described are successful in

improving maternal, obstetric, and offspring outcomes and whether they have the real translational potential to be a therapeutic option for obese pregnant women. Pragmatic

study designs that encourage and support pregnant women and that can adapt to meet the cultural requirements of the local population, are essential.

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50 Lifestyle interventions to reduce risk of diabetes among high-risk pregnant and postpartum women

Lisa Chasan-Taber

Background

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy with a prevalence rate varying from 1% to 20% depending on the population studied and diagnostic criteria applied.^{1,2} With the recent adoption of the International Association of Diabetes and Pregnancy Study Groups Consensus Panel diagnostic criteria, it is estimated that 18% of pregnant women will be diagnosed with GDM.¹ Obesity is strongly associated with risk of GDM,³ and it is expected that the incidence of GDM among women of reproductive age will further increase as the prevalence of obesity continues to rise among this age group.

GDM is related to short- and long-term adverse health outcomes for the mother. Compared with women with healthy pregnancies, women with histories of GDM have elevated CVD risk factors including higher blood pressure, triglyceride levels, and lower HDL.⁴ Consistent with these findings, a meta-analysis found that GDM confers a seven-fold risk for future type 2 diabetes⁵ and up to one-third of women with type 2 diabetes have previously been diagnosed with GDM.⁶

According to a systematic review, the highest-risk period for the development of type 2 diabetes is within the first 5 years after a GDM pregnancy.⁷ Therefore, both GDM and milder glucose intolerance in pregnancy identify women who are at high risk for subsequent glucose intolerance and type 2 diabetes and offer the opportunity to implement interventions to decrease such risk.^{7,8} However, while lifestyle interventions involving exercise and a healthy diet in high-risk adults have been found to reduce progression to type 2 diabetes by more than 50%,^{9–12} little attention has been given to the potential benefits of such strategies in women with a history of GDM.

Therefore, the goal of this chapter is to provide a comprehensive overview of the randomized controlled trials of

lifestyle interventions designed to reduce the risk of diabetes or diabetes risk factors among women with a history of GDM. The chapter first describes the impact of the lifestyle interventions on the incidence of type 2 diabetes and biomarkers of insulin resistance, weight change, and healthy behaviors such as physical activity, diet, and breastfeeding. The chapter then goes on to describe the study design and methods of new randomized trials that have been recently launched. The chapter concludes with recommendations for future research and practice.

Methods

We conducted a literature search of PubMed for English-language studies of randomized controlled trials of lifestyle interventions among women with a history of GDM. Only published peer-reviewed journal articles of original research in the English language were included. Keyword searches included lifestyle intervention, randomized controlled trial, type 2 diabetes, prevention, diet, physical activity, postpartum, pregnancy, weight retention, gestational diabetes mellitus, and health behaviors. Additional relevant articles cited in the reference lists of identified papers were retrieved manually.

In total, nine randomized controlled trials of lifestyle interventions conducted among women with a history of GDM were identified to fulfill the eligibility criteria (Tables 50.1 and 50.2).^{13–21} Of these studies, two examined the impact of the lifestyle intervention on subsequent incidence of diabetes,^{18,21} and four examined the impact on postpartum biomarkers of insulin resistance.^{15–17,20} In terms of other risk factors for diabetes, all with the exception of one study²¹ examined the impact of the lifestyle intervention on weight change and physical activity. Four of the trials examined the impact on diet.^{14,15,19,20} Only one study to date reported the impact on breastfeeding.¹⁴

Table 50.1 Randomized trials of lifestyle interventions to reduce risk of type 2 diabetes among women with gestational diabetes mellitus: Study designs

Source	Name	Design	Pilot	Population	Intervention	Mode	Goals
Cheung et al. ¹³		RCT; FU: 12 months	Pilot	43 women with previous GDM <4 years. previously; Australia	Exercise intervention vs. usual care control	Individualized in person; telephone; mailings	PA: 150 minute/week or 10,000 steps/day for 5 days/week
Ferrara et al. ¹⁴	Diet, Exercise, and Breastfeeding Intervention	RCT; FU: 12 months	Pilot	197 women with current GDM; California	Lifestyle intervention (diet, exercise, breastfeeding) vs. usual care control	Individualized in person; telephone	Weight, return to prepregnancy weight if normal, lose 5% of prepregnancy weight if overweight; PA, 150 minute/week of moderate intensity or harder; diet, ≤25% calories from fat; breastfeeding, exclusively for 6 months
Hu et al. ¹⁵	Tianjin Gestational Diabetes Mellitus Prevention Program	RCT; 1 year	Preliminary results	404 women with previous GDM from 2005 to 2009; China	Lifestyle intervention (diet and exercise) vs. usual care control	Individualized in person	Weight, no weight loss if normal weight, lose 5%–10% of prepregnancy weight if BMI ≥ 24 kg/m ² through reduction of ≥10% total calories; PA, 150 of moderate intensity or harder; diet, TF <30%, fiber 20–30 g/day, % calories from fat
Kim et al. ¹⁶		RCT; FU: 13 weeks	Pilot	49 women with previous GDM within past 3 years; Michigan	Exercise intervention vs. usual care control	Web based	Steps: up to 10,000 steps/day
McIntyre et al. ¹⁷		RCT; FU: 12 weeks	Pilot	28 women with previous GDM 6 weeks postpartum; Australia	Exercise intervention vs. usual care control	Individualized in person; telephone	PA: 150 minute/week
Rather et al. ¹⁸	Diabetes Prevention Program	RCT; FU: 2.8 years		350 women with previous GDM and current elevated glucose levels from the DPP; United States	Lifestyle intervention (diet and exercise) vs. placebo	Individualized in person; group sessions	Weight, reduction ≥7% of initial body weight; diet, low calorie, low fat; PA, moderate intensity ≥150 minute/week
Reinhardt et al. ¹⁹		RCT; FU: 6 months	Pilot	38 women following GDM diagnosis; Australia	Lifestyle intervention (diet and exercise) vs. usual care control	Telephone; mailings	Healthy eating and PA
Shyam et al. ²⁰		RCT; FU: 6 months		77 women with previous GDM within 2 months; Malaysia	Low GI diet vs. usual care control	In person; text messaging, e-mails	Weight, 5%–7% reduction in body weight if BMI > 23 and maintenance if normal; PA, moderate intensity for 30 minutes/day five times per week
Wein et al. ²¹		RCT; FU: 796 person-years (median 51 months)		200 women with previous GDM from 1989 to 1991 and subsequent IGT	Diet intervention vs. control	Telephone; mailings	Diet, healthy eating; PA, exercise (30 minutes three times per week)

Abbreviations: RCT, randomized clinical trial; FU, follow-up; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; PA, physical activity; FC, fasting glucose; GI, glycemic index; BMI, body mass index.

Table 50.2 Randomized trials of lifestyle interventions to reduce risk of type 2 diabetes among women with gestational diabetes mellitus: Findings

Author	Name	Impact on type 2 diabetes	Impact on biomarkers of insulin resistance	Impact on weight	Impact on PA	Impact on diet	Impact on breastfeeding
Cheung et al. ¹³		NA	NA	BMI (kg/m ²): 28 (95% CI: 23.9, 34.3) vs. 25.5 (95% CI: 22.5, 28.7), $p = 0.14$	Steps (% achieving goal), 30.8 vs. 17.6 $p = 0.34$; PA (% achieving goal), 70.0 vs. 57.9, $p = 0.51$	NA	
Ferrara et al. ¹⁴	Diet, Exercise, and Breastfeeding Intervention	NA	NA	Weight (% achieving goal): 37.5% vs. 21.4%, $p = 0.07$	PA (difference in mean change in minute/week): 25.3, $p = 0.91$	Fat (% difference in mean change) -3.6, $p = 0.002$	Breastfeeding (difference in % partially or exclusively breastfeeding): 15%, $p = 0.09$
Hu et al. ¹⁵	Tianjin Gestational Diabetes Mellitus Prevention Program	NA	FG (change in mmol/L), -0.09 ± 0.52 vs. -0.09 ± 0.6, $p = 0.97$; insulin (change in pmol/L), -11.8 ± 27.4 vs. -3.2 ± 31.2, $p = 0.004$	Weight change, -1.4 ± 3.44 kg vs. -0.21 ± 3.52 kg (0.3%), $p = 0.001$; BMI change, -0.50 ± 1.41 kg/m ² vs. -0.09 ± 1.37 kg/m ² , $p = 0.004$	LTPA (% increased): 59.4% vs. 26.9%, $p < 0.001$	Fat (% decrease), 77.1 vs. 68.9, $p = 0.064$; fiber (% increase), 59.5 vs. 47.4, $p = 0.012$	NA
Kim et al. ¹⁶		NA	FG (change in mmol/L), -0.046 vs. 0.038, $p = 0.65$; 2-hour glucose on 75 g OGTT (change in mmol/l), -0.48 vs. -0.42, $p = 0.91$	Weight (change in kg): -0.14 kg vs. -1.5 kg, $p = 0.13$	PA (% moderate intensity): 58 vs. 47, $p = 0.51$	NA	NA
McIntyre et al. ¹⁷		NA	FG (change in mmol/L), 0.25 ± .56 vs. 0.12 ± 0.42, NS; insulin (change in nU/mL), 1.49 ± 4.23 vs. 0.06 ± 3.89, NS	Change in weight (kg): 0.97 + 3.7 vs. 0.22 + 4.2 NS	PA (median [range] increase in planned PA minutes/week), 60 (0–540) vs. 0 (0–580); $p = 0.234$; walking, NS	NA	NA

(Continued)

Table 50.2 (Continued) Randomized trials of lifestyle interventions to reduce risk of type 2 diabetes among women with gestational diabetes mellitus: Findings

Author	Name	Impact on type 2 diabetes	Impact on biomarkers of insulin resistance	Impact on weight	Impact on PA	Impact on diet	Impact on breastfeeding
Ratner et al. ¹⁸	Diabetes Prevention Program	Diabetes: 53% risk reduction vs. placebo, $p = 0.002$	NA	Weight (change in kg): -5.13 ± 0.43 vs. approx. 0 in placebo at 6 months; -1.6 ± 0.80 vs. approx. 0 in placebo at 3 years	PA (change in hour/week): 1.5 hour/week vs. NA in year 1; <0.5 vs. NA in year 3	NA	NA
Reinhardt et al. ¹⁹		NA	NA	BMI (difference in change in kg/m^2), -1.5 (95% CI: -2.8 , -0.1); weight (difference in change in kg), -4.0 (95% CI: -7.6 , -0.5)	LTPA (change in minutes/day): 11 (95% CI: 1, 22)	Total fat (change in g/day), -19 (95% CI: -37 , -1); GL (unit change), -26 (95% CI -48 , -4)	NA
Shyam et al. ²⁰		NA	Glucose, 2 hours post 75 g OGTT (median mmol/L, IQR), -0.2 (2.8) vs. 0.8 (2.0), $p = 0.025$; insulin (<2 $\mu\text{U}/\text{L}$), 61.5% vs. 52.6%, $p = 0.228$	Weight (% achieving goal): 33% vs. 8%, $p = 0.01$	PA (median MET-minute/week, IQR): 933 (1403) vs. 965 (857), $p = 0.908$	Fat (g), 58 ± 18 vs. 53 ± 16 , $p = 0.695$ for difference in change; fiber (g), 17 ± 4 vs. 13 ± 4 , $p = 0.02$ for difference in change; GI, 57 ± 5 vs. 64 ± 6 , $p = 0.033$ for difference in change	
Wein et al. ²¹	Diabetes	(annual incidence rate): 6.1% vs. 7.3% (incidence rate ratio = 0.83, 95% CI: 0.47, 1.48)	NA	NA	NA	NA	

Abbreviations: RCT, randomized clinical trial; FU, follow-up; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; PA, physical activity; FG, fasting glucose; GI, glycemic index; LTPA, leisure time physical activity.

Results

Type 2 diabetes and biomarkers of insulin resistance

Among the nine randomized controlled trials conducted among women with GDM, two evaluated the impact of a lifestyle intervention on subsequent incidence of diabetes,^{18,21} and four examined the impact on postpartum biomarkers of insulin resistance (Table 50.2).^{15–17,20} The most successful intervention to date in terms of impact on subsequent diabetes was observed by the Diabetes Prevention Program (DPP),⁹ a multicenter randomized trial of an intensive lifestyle intervention conducted among a population of adults who had elevated fasting and postload plasma glucose concentrations. Goals of the lifestyle intervention were at least a 7% reduction in enrollment weight; a low-calorie, low-fat diet; and at least 150 minutes/week of moderate-intensity physical activity. In a subset of this population limited to women with a self-reported history of GDM ($n = 350/2190$), Ratner et al.¹⁸ found that the incidence of type 2 diabetes in those randomized to the lifestyle intervention was 7.4/100 person-years, compared with 15.2/100 person-years in the placebo group, for a 53% reduction in incidence ($p = 0.002$). However, this study involved an intensive intervention not easily administered in a clinical setting and was conducted an average of 12 years after GDM diagnosis such that intervening lifestyle factors and subsequent pregnancies may have modified findings. For example, women with early postpartum conversion to diabetes, and therefore at highest risk, were not eligible.

In the second trial evaluating the impact of the intervention on subsequent diabetes, Wein et al.²¹ randomized 200 women with previous GDM and subsequent impaired glucose tolerance to an intensive dietary intervention targeting healthy eating and regular exercise (i.e., 30 minutes for three times per week) or to routine dietary advice. Follow-up continued for a median of 51 months. Women randomized to the dietary intervention had an annual incidence rate of type 2 diabetes of 6.1% as compared to 7.3% in the control arm for an incident rate ratio of 0.83 (95% confidence interval (CI) 0.47–1.48), which was not statistically significant. As with the study by Ratner et al., this trial was conducted years after GDM diagnosis and therefore faced the same limitations described earlier.

Of the four studies that evaluated the impact of the lifestyle intervention on biomarkers of insulin resistance,^{15–17,20} two observed a statistically significant positive impact on blood glucose measures.^{15,20} For example, Hu et al. randomized 404 participants in the Tianjin Gestational Diabetes Mellitus Prevention Program (TGDMPP) diagnosed with GDM from 2005 to 2009 to either a lifestyle intervention or a control group.¹⁵ The goals of the intervention included weight loss of 5%–10% of pregnancy weight if overweight through reduction of at least 10% of total calories, participation in 150 minutes/week of moderate-intensity activity or harder, and reduction of total fat to less than 30% of calories. Interim 1-year results indicate that women in the intervention group had a greater reduction in plasma

insulin levels (-11.8 ± 27.4 pmol/L) as compared to those in the control arm (-3.2 ± 31.2 pmol/L, $p = 0.004$). The authors also observed the suggestion of a positive impact of the intervention on fasting glucose levels.

Similar findings were observed by Shyam et al., who randomized 77 Asian women who had been diagnosed with GDM in the prior 2 months to a low-glycemic-index dietary intervention or to a usual care control.²⁰ Goals of the intervention were a 5%–7% reduction in body weight if prepregnancy BMI was greater than 23 kg/m² and moderate-intensity physical activity of 30 minutes at least five times per week. At 6 months of follow-up, the intervention group had significantly greater decreases in 2-hour postload blood glucose after 75 g oral glucose tolerance test (median [IQR, inter-quartile range]: -0.2 [2.8] mmol/L) as compared to the control arm (0.8 [2.0] mmol/L), $p = 0.025$. The suggestion of a beneficial impact on plasma insulin was not statistically significant.

Weight change

With the exception of one study,²¹ all of the intervention studies conducted among women with prior GDM examined the impact on weight (Table 50.2). It is important to note here that four of these studies^{14,17,19,20} had conducted among women with current GDM or very recent (e.g., within the past 2 months) GDM, and therefore, focused on postpartum weight loss and return to prepregnancy weight. The majority observed a statistically significant positive impact of the intervention.^{15,18–20}

In a feasibility study, Ferrara et al. randomized women with a current diagnosis of GDM in late pregnancy to a lifestyle intervention that continued for 12 months postpartum or to a usual care control arm.¹⁴ Goals of the intervention were to return to prepregnancy weight, if it was normal, or achieve a 5% reduction from prepregnancy weight if overweight. The proportion of women who reached the postpartum weight goal was higher, although not statistically significantly, in the lifestyle intervention arm as compared to the usual care arm (37.5% vs. 21.4%, absolute difference 16.1%, $p = 0.07$). However, in the subgroup of women not exceeding gestational weight gain guidelines, the lifestyle intervention was more effective (difference in the proportion of women meeting the weight goals: 22.5%, $p = 0.04$).

Findings of similar magnitude were observed by Hu et al. in the TGDMPP.¹⁵ Specifically, the authors found a 1.4 kg (2.1%) weight loss in the intervention arm at 1 year of follow-up compared to a 0.21 kg (0.3%) weight loss in the control arm ($p = 0.001$), as well as a positive impact on BMI, body fat, and waist circumference. Ratner et al. in the DPP observed a weight loss of -5.13 ± 0.43 kg in the lifestyle arm after 6 months that decreased to a weight loss of -1.6 ± 0.80 kg at year 3 of follow-up.¹⁸ Shyam et al. found that 33% of women in the intervention arm achieved the prespecified weight loss goal as compared to 8% in the control arm ($p = 0.01$).²⁰

Physical activity

All of the trials with the exception of one²¹ examined the impact of a lifestyle intervention on physical activity among women diagnosed with GDM (Table 50.2). Of these, three^{15,18,19} observed a statistically significant impact on one or more measures of activity, while the others tended to observe the suggestion of a beneficial effect. For example, Reinhardt et al. randomized 38 women in rural Australia following their diagnosis of GDM into an exercise intervention or a control arm.¹⁹ At 6 months follow-up, the intervention group increased leisure physical activity compared to the control group by 11 minutes/day (95% CI: 1, 22); however, changes in total physical activity levels were not statistically significantly different between groups.

Hu et al. in the TGDMP observed a similar positive impact on leisure time physical activity, with a percent increase of 59.4% in the intervention arm as compared to a 26.9% increase ($p < 0.001$) in the control arm, but no significant impact on walking.¹⁵ Ratner et al. in the DPP observed an increase of approximately 1.5 hours/week in moderate-intensity physical activity after 1 year, which diminished to an increase of less than 30 minutes of physical activity by year 3.¹⁸

Dietary factors

Four of the trials examined the impact of the lifestyle intervention on diet,^{14,15,19,20} and all observed a statistically significant beneficial impact on one or more dietary components. For example, in the pilot feasibility study by Ferrara et al., the authors observe a percent difference in mean change in fat of -3.55% between the lifestyle arm and the control arm ($p = 0.002$).¹⁴ Hu et al. in the TGDMP observed that the lifestyle arm had 77.1% decrease in energy from fat as compared to a 68.9% decrease in the control arm ($p = 0.064$).¹⁵ Reinhardt et al.¹⁹ in their 6-month pilot study in Australian women observed a change in total fat between arms of -19 g/day (95% CI: $-37, -1$). A beneficial impact of the lifestyle intervention on fiber was observed by Hu et al. and Shyam et al.

Breastfeeding

Only one study to date examined the impact of the lifestyle intervention on breastfeeding among women with prior GDM.¹⁴ Specifically, Ferrara et al. found that the difference in percent of women partially or exclusively breastfeeding between the intervention and control arms was 15% ($p = 0.09$).

Newly launched randomized trials of lifestyle interventions to prevent diabetes among women with GDM

The following section provides an overview of the recently launched lifestyle intervention studies among women with GDM. Five trials are currently ongoing (Table 50.3).^{22–24}

Berry et al.²² are conducting a randomized controlled trial among 100 African-American, non-Hispanic white, and bilingual Hispanic women between 22 and 36 weeks of pregnancy who are diagnosed with GDM in North Carolina. Women are randomized in late pregnancy (22–36 weeks gestation) to a 14-week lifestyle intervention including diet and physical activity or to a wait-listed control group. Follow-up will continue to 10 months postpartum. Primary outcomes will include fasting blood glucose and BMI from baseline to 10 months postpartum. Secondary maternal outcomes will include clinical, adiposity, health behaviors, and self-efficacy outcomes.

Chasan-Taber et al. are conducting Estudio Parto (Project Aiming to Reduce Type two diabetes), a randomized controlled trial in western Massachusetts.²³ A total of 300 Hispanic prenatal care patients who screen positive for GDM at 24–28 weeks gestation are randomized to a culturally and linguistically modified, individually tailored lifestyle intervention or to a health and wellness comparison control group. Follow-up will continue to 12 months postpartum. The intervention is delivered via three in-person sessions, telephone booster calls, and mailed materials. Targets of the intervention are (1) postpartum weight reduction to prepregnancy weight if prepregnancy BMI was in the normal range or a 5% reduction from prepregnancy weight if prepregnancy BMI was overweight/obese, (2) at least 150 minute/week of moderate-intensity physical activity, and (3) reduction in postpartum total caloric intake via reduced consumption of popular calorie dense foods, reduced portion size, modifications in ethnic recipes, and higher fruit and vegetable intake. Primary outcomes will include postpartum weight loss, biomarkers associated with insulin resistance, other cardiovascular risk factors, and the adoption and maintenance of healthy physical activity and dietary behaviors.

Ferrara et al. are conducting the Gestational Diabetes' Effects on Moms study,²⁴ a cluster randomized clinical trial of 44 medical facilities at Kaiser Permanente Northern California. A total of 2320 women with a GDM diagnosis between March 2011 and March 2012 are randomized to either the intervention or usual care conditions. Follow-up will continue to 12 months postpartum. The intervention is a DPP-derived print/telephone lifestyle intervention. Primary outcomes will include the achievement of postpartum weight goals and total weight change. Secondary outcomes include postpartum glycemia, blood pressure, depression, percent of calories from fat, total caloric intake, and physical activity levels.

Infanti et al.²⁵ are conducting Croi MyAction, a two-group, parallel randomized controlled trial for women with prior GDM. A total of 54 women with a history of GDM and persistent postpartum glucose dysfunction are randomly assigned to an intervention group or to a control arm. Follow-up will continue to 1 year postintervention. The lifestyle intervention is delivered via in-person sessions including one-on-one sessions, group exercise, and education programs. Primary outcomes include fasting plasma glucose levels on a 75 g oral glucose tolerance test.

Table 50.3 Newly launched randomized trials of lifestyle interventions to reduce risk of type 2 diabetes among women with gestational diabetes mellitus

Author	Name	Design	Population	Intervention	Mode	Goals	Outcomes
Berry et al. ²²		RCT; FU: 10 months	100 ethnically/racially diverse women with current GDM; North Carolina	Lifestyle intervention (diet and exercise) vs. control	Individualized in person; group sessions; text messaging	Healthy behaviors	Primary, FPG, BMI; secondary, clinical, adiposity, behaviors, self-efficacy
Chasan-Taber et al. ²³	Estudio Parto	RCT; FU: 12 months	300 Hispanic women with current GDM; Massachusetts	Lifestyle intervention (diet and exercise) vs. health and wellness control	Individualized in person; telephone; mailings	Weight, return to prepregnancy weight if normal weight, lose 5% of prepregnancy weight if overweight; PA, 150 minute/week of moderate intensity or harder; diet, ≤25% calories from fat	Primary, postpartum weight retention, biomarkers of insulin resistance, and CVD; secondary, exercise, diet
Ferrara et al. ¹⁴	Gestational Diabetes' Effects on Moms study	RCT; FU: 12 months	2320 women with a GDM diagnosis between March 2011 and March 2012; California	Lifestyle (diet, exercise) vs. usual care control	Telephone; mailings	Weight, return to prepregnancy weight if normal weight, lose 5% of prepregnancy weight if overweight or obese; PA and diet, individualized goals	Primary, postpartum weight; secondary, postpartum glycemia, blood pressure, depression, % calories from fat, total caloric intake; PA levels
Infanti et al. ²⁵	Croi MyAction	RCT; FU: 12 months	54 women with previous GDM and persistent postpartum glucose dysfunction; Ireland	Lifestyle intervention (diet and exercise) vs. control	Individualized in person; group	Healthy lifestyle	Primary (FPG), secondary (insulin resistance, diet adherence, weight, and BMI), PA and fitness, lipid profile, psychological factors
Shih et al. ²⁶	Mothers After Gestational Diabetes in Australia Diabetes Prevention Program	RCT; FU: 12 months	574 women with GDM in most recent pregnancy; Australia	Lifestyle intervention (diet and exercise) vs. control	Individualized in person; group sessions; telephone	Weight, reduce >5%; PA ≥30 minute/day in moderate intensity; diet, fat intake <30%; fiber >15 g/1000 kcal	Primary, diabetes risk; secondary, psychosocial, QOL, CVD risk Factors

Abbreviations: RCT, randomized clinical trial; FU, follow-up; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; PA, physical activity; FPG, fasting glucose; Gl, glycemic index; LTPA, leisure time physical activity; BMI, body mass index; kcal, kilocalories; QOL, quality of life; CVD, cardiovascular disease.

Shih et al. are conducting the Mothers After Gestational Diabetes in Australia Diabetes Prevention Program, a randomized controlled trial among 574 women with a diagnosis of GDM in their most recent pregnancy.²⁶ Women are randomized to 12-month diabetes prevention program or to a usual care control group. The intervention is delivered via in-person and group sessions and telephone. Follow-up continues for 12 months. Primary outcomes include incidence of diabetes, and secondary outcomes include cardiovascular risk factors and psychosocial and quality of life factors.

Discussion

Postpartum lifestyle interventions are critical in light of recent findings from long-term follow-up studies that a significant proportion of women with GDM go on to develop type 2 diabetes, especially during the first decade after the index pregnancy.⁵ With the growing rates of diabetes and obesity in US women, evidence regarding the effectiveness of lifestyle modification for the prevention of diabetes in women with GDM is critical. Therefore, GDM offers an important opportunity for the development, testing, and implementation of clinical strategies for the prevention of subsequent type 2 diabetes.²⁷ Such protocols can capitalize on the teachable moment of pregnancy²⁸ and empower women to make postpartum lifestyle changes.

To date, the majority of randomized controlled trials of lifestyle interventions in women with GDM designed to prevent type 2 diabetes have been limited to pilot or feasibility studies. However, preliminary findings suggest that such interventions can improve postpartum biomarkers of insulin resistance and other diabetes risk factors in women with a history of GDM. Specifically, the trials conducted to date have observed favorable impacts on fasting glucose, insulin, postpartum weight, leisure time physical activity, and intake of total fat, fiber, and glycemic load. Only one study to date examined the impact on breastfeeding and found the suggestion of a beneficial impact.¹⁴

While evidence is rapidly accumulating that behavior in the postpartum period may be critical in the prevention of longer-term progression toward diabetes, lifestyle changes can be difficult to implement in these critical years after delivery. Postpartum women may be faced with the pressures of caring for a new baby in addition to their existing household and caregiving responsibilities. Recent qualitative data show that having young children is a major barrier to an active lifestyle in the first 12 months postpartum.²⁹ Other qualitative and quantitative studies indicate a number of barriers to physical activity during postpartum, including physical discomfort, parenting duties, tiredness, lack of time, not prioritizing their health over other competing responsibilities, and lack of spousal/partner support.³

A second challenge to implementing behavior change in the postpartum period is the relatively low perceived risk of future diabetes among women with recent GDM. A review³⁰ of studies examined the risk perceptions and health behaviors of women with previous GDM. The authors found

low-risk perceptions for future type 2 diabetes and suboptimal levels of physical activity and fruit and vegetable intake. The majority of studies reveal a distinct knowledge-behavior gap among this population as well as a lack of knowledge regarding necessary lifestyle modifications.³⁰

Promising strategies to address these challenges can be found in recent studies that have found a number of enablers to postpartum lifestyle changes including social support.³¹ Dasgupta et al.³² conducted focus groups among women within 5 years of a GDM diagnosis. Participants stated that their participation in a diabetes prevention program would be enhanced by face-to-face interactions with professionals and peers, provision of childcare support, and inclusion of spouses/partners. Therefore, interventions that integrate the entire family and influence family members, along with the participant, to adopt health promoting behaviors may be particularly successful.

In this vein and to address transportation barriers, home-based interventions conducted via mail, telephone, the Internet/e-mail, and text messaging or involving home visits by health educators may be more feasible and acceptable to women in the postpartum period. For example, several recent trials that relied largely on the Internet, mail, or telephone have observed promising results.^{16,19,21} Furthermore, there is evidence that Internet-based lifestyle interventions can increase exercise in a general postpartum population.³³ However, at the same time, Internet access may be a barrier as women with GDM tend to have lower socioeconomic status than women without GDM.³⁴

Weight loss interventions that begin during pregnancy may be more effective than those initiated only in the postpartum period given the strong association between GWG and postpartum weight retention and the fact that it may be difficult to reduce postpartum weight retention without first preventing excessive gestational weight gain during pregnancy.³⁵ Two of the published trials began in late pregnancy^{14,19} and suggest that such protocols can have a beneficial impact on gestational weight gain as well as prepare women for postpartum changes. Consideration should also be given to translating such programs to clinical care. In their newly launched study,²⁴ Ferrara et al. are evaluating whether delivering a diabetes prevention program at the health system level is able to successfully reach women with prior GDM.

Breastfeeding has been associated with reduced blood glucose levels and a reduced incidence of type 2 diabetes among women with a history of GDM.³⁶ However, only one of the nine published trials included breastfeeding as one of their goals.¹⁴ Future trials should focus on promoting a combination of breastfeeding, diet, and physical activity.

Finally, rates of progression to type 2 diabetes vary by ethnicity, with, for example, Asian and Hispanic women having higher rates of progression than non-Hispanic white women.³⁷ At the same time, Hispanic women have higher rates of being overweight/obesity when entering pregnancy and are more likely to be sedentary than non-Hispanic white women.³⁷ Future studies should focus on these high-risk groups. One newly launched study²³ is being conducted in

Hispanic women only and will evaluate whether a culturally modified intervention will be effective in reducing diabetes risk in Latinas with GDM.

In summary, trials of diabetes prevention programs among high-risk pregnant and postpartum women are sparse. Collectively, the prior body of evidence suggests that such lifestyle interventions, if delivered to women with a history of GDM, would have the potential to delay or prevent one-sixth of type 2 diabetes cases in the female population.³⁸ Larger, well-designed controlled randomized trials are needed to assess the effects of lifestyle interventions on

preventing subsequent progression to type 2 diabetes among women with GDM. Such interventions that focus on the acquisition of healthy lifestyle skills in late pregnancy and postpartum have a high potential for preventing the intergenerational cycle of diabetes in this high-risk population.

Acknowledgment

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51 Can fetal macrosomia be predicted and prevented?

Maria Farren and Michael Turner

Introduction

There is no consensus about the definition of macrosomia. Some authors prefer large for gestational age (LGA) (>90th%) and others birth weights (BW) of ≥ 4.0 kg, ≥ 4.1 kg, or ≥ 4.5 kg.¹⁻³ The American College of Obstetricians and Gynecologists (ACOG) defines macrosomia as an infant with a BW of ≥ 4.5 kg irrespective of gestational age or other demographic characteristics.⁴ The use of centiles depends on the pregnancy being accurately dated by ultrasound, and this may not be possible in resource-poor settings. Macrosomia based on BW > 4.0 kg in our hospital would include 12%–13% of neonates.⁵ Adverse clinical consequences in this group are uncommon. This definition makes little sense because adverse consequences for a BW of 4.0–4.5 kg may occur, and any interventions have not been shown to improve clinical outcomes.

For the purpose of this chapter, we are defining fetal macrosomia as a BW of ≥ 4.5 kg. This is based on studies showing increased fetal and maternal trauma at the delivery of a baby weighing ≥ 4.5 kg.⁶ The definition of macrosomia as ≥ 4.5 kg represents 2%–3% of our neonatal population. The 4.5 kg limit is only appropriate for term babies and can be criticized for being arbitrary as the incidence of shoulder dystocia rises between BWs of 4.0 and 4.25 kg. It could be argued that 4.25 kg be used as the cutoff value.^{7,8} However, the ≥ 4.5 kg limit defines unequivocally and unambiguously a high-risk group that may benefit from accurate diagnosis and management over the peripartum period.⁸

The macrosomic fetus is at risk of perinatal complications such as shoulder dystocia, brachial plexus injury, clavicular fracture, and meconium aspiration.^{3,9-12} In the neonatal period, macrosomic infants are at risk of hypoglycemia, hyperbilirubinemia, and hypomagnesemia.¹³ The mother of a macrosomic infant is at increased risk of prolonged labor, operative vaginal delivery, perineal trauma, and cesarean section.^{9,12,14,15}

The effect of BW on neonatal risk, morbidity, and mortality was studied in a retrospective review in Birmingham, AL, between 1995 and 1997.⁶ From this review, it was concluded that babies ≥ 4.5 kg were at greater risk of labor complications

such as cesarean section, shoulder dystocia, brachial plexus injuries, and neonatal morbidity. Based on the finding of this study, a grading system for macrosomia was proposed. Grade I macrosomia was defined as 4000–4499 g, grade II macrosomia as 4500–4999 g, and grade III macrosomia as ≥ 5000 g. Labor complications, birth injuries, and newborn morbidity increased with increasing gradation. It was found that perinatal mortality was increased in neonates ≥ 5000 g.⁶

Incidence

The incidence of macrosomia is widely reported to be increasing.^{16,17} However, some of this evidence is more than 20 years old. The incidence of fetal macrosomia in our unit has decreased over 20 years whether the definition used is either ≥ 4.0 or ≥ 4.5 kg (Figure 51.1).

In the Republic of Ireland, the incidence of macrosomia has not increased over the last 10 years. The rate of the macrosomia (infants ≥ 4.5 kg) has been 2.5%–2.9% (Figure 51.2). The mean BW for singleton births in the Irish population from 1990 to 2012 shows little variation (Figure 51.3).

Similarly in the United States, the incidence of macrosomia across all subgroups is decreasing (Figure 51.4), despite rising obesity rates.¹⁸

The incidence of macrosomia in Scandinavia may be increasing. This is reflected in studies from Sweden and Denmark. In Sweden in 2001, a large retrospective study reviewed all birth records from 1992 and 2001. This included 874,163 live, term, singleton births. They found that mean BW increased from 3596 to 3631 g and the percentage of infants weighing > 4500 g or more increased from 3.7% to 4.6%.¹⁹ This study cites an increasing average maternal BMI and decreasing smoking rate over the same time period as contributing factors to this increase. However, the increase in mean BMI is hardly significant clinically and may reflect the timing of obstetric interventions at term, e.g., cesarean section or induction of labor.

In Denmark a retrospective study in 2001 reviewed all term singleton deliveries from 1990 to 1999. This included 26,392 infants. Similarly, they found that mean BW increased,

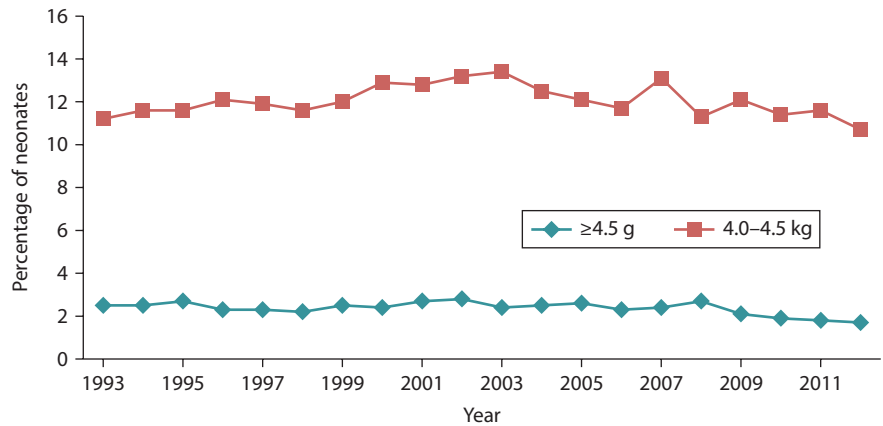


Figure 51.1 Birth weights in 1992–2012, Coombe Women and Infants University Hospital.

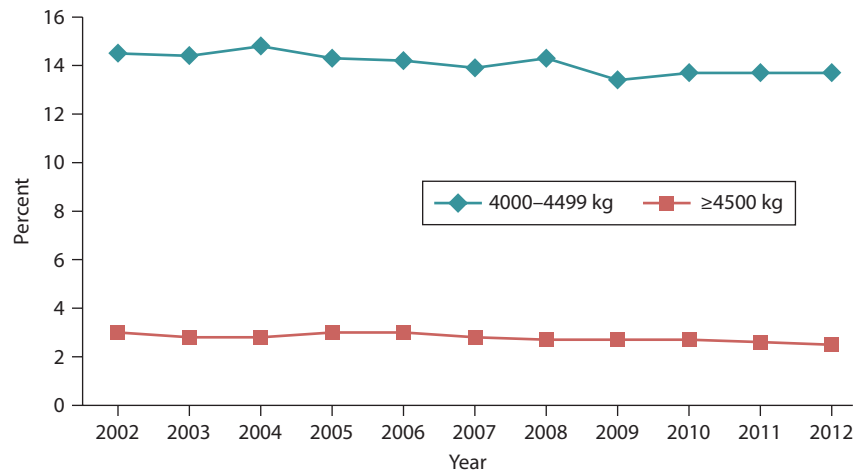


Figure 51.2 Percentage of babies born in the Republic of Ireland in 2002–2012, ESRI/NPRS Perinatal Statistics Report 2003–2012.

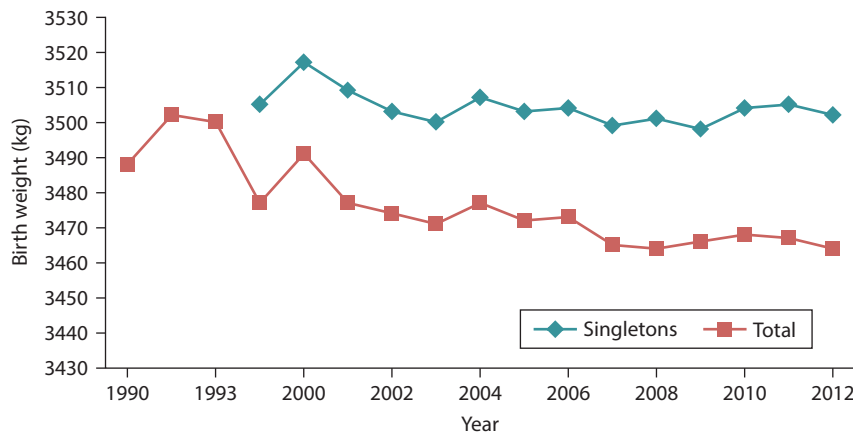


Figure 51.3 Mean birth weight in Ireland, ESRI/NPRS Perinatal Statistics Report.

as did the proportion of infants weighing 4000–4249 g, 4250–4499 g, and 4500 g or more.²⁰ However, it is worth noting that within their study, only 60.2% had their pregnancies dated by early pregnancy ultrasound. The remaining subjects had their pregnancies dated on the basis of the last menstrual period or on the gestational age recorded as booking. This may explain the apparent increase in BW.

Overall, it is observed that the incidence of macrosomia has remained stable over the last 10–15 years. Anecdotally babies are getting bigger. However, with the possible exception of Scandinavia, this is not the case as is reflected in our analysis at local, national, and international level. Commentary in the literature is fraught with discrepancies, assumptions, and inaccurate measurements of gestation at

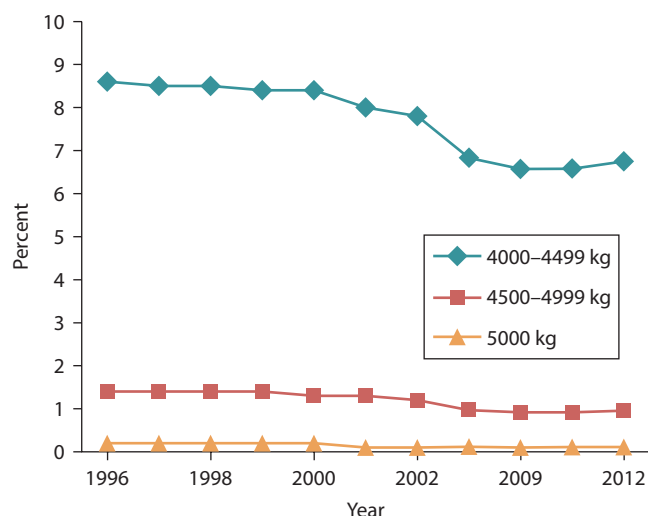


Figure 51.4 Percentage of singleton births in all macrosomic groups in the United States in 1996–2012, National Vital Statistics, CDC.

recruitment and delivery. These discrepancies illustrate the importance of accurate dating of a pregnancy so that any diagnosis of macrosomia is not erroneous.

The reason for any decreasing trends in fetal macrosomia is multifactorial. The increasing rate of assisted reproduction has led to an increased number of twin and multiple pregnancies.²¹ Such an increase of multiple pregnancies leads to a decrease in the overall BW as multiple pregnancies tend to be delivered earlier and overall weigh less than their singleton counterparts.

The diagnosis and management of gestational diabetes mellitus (GDM) also may account for the plateau in the BWs. The criteria for screening remain controversial, but even with selective screening, more women are being diagnosed with GDM.²² The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial revealed the effects of mild hyperglycemia on fetal size and has subsequently led to changes in the parameters once considered for the diagnosis of GDM.²³

Larger numbers of women being screened for GDM may lead to earlier intervention and this improves glycemic control. The control of blood glucose levels can be achieved through diet, oral hypoglycemics, and subcutaneous insulin. The overall effect of treatment modalities is stricter glycemic control and subsequent reduction in BW.²⁴ This may also explain the plateau in the number of macrosomic infants. In the United States, there is a trend toward universal screening for GDM. Therefore, even greater numbers of women are diagnosed with GDM, and their pregnancies are managed ideally within strict glycemic control.²⁴

In addition to the regulation of hyperglycemia, the pregnancy complicated by GDM is unlikely to progress past 38 weeks gestation especially in the case of insulin-dependent GDM.²⁵ As a result, these fetuses are not being given the opportunity for a growth surge in the latter part of pregnancy and in the postdates period. This may impact on the overall percentage of macrosomic infants.

For a variety of reasons, the rate of induction of labor at term is increasing in both primiparous and multiparous women.^{26,27} Induction before term will result in the delivery of an infant much smaller than if that infant had been left to deliver at term or beyond, in the postdates period.

Indeed, the suspicion of macrosomia may be given as a reason for induction of labor. This diagnosis, often made on clinical examination or ultrasound, is fraught with error and interobserver variation. However, it can drive clinicians to plan an induction before term, again resulting in the delivery of a lighter infant than would have been delivered after term.

Risk factors

The risk factors for macrosomia are either modifiable or unmodifiable (Table 51.1). Unmodifiable risk factors include maternal age, parity, ethnicity, parental height, gender of the fetus, and a history of a previous LGA infant.

The effect of maternal age was demonstrated in a retrospective American review in 1985.¹⁵ A total of 574 infants weighing <4500 kg were compared to a control sample of 18,739 infants weighing 2500–3499 kg. This study found that women delivering macrosomic infants were older and of higher parity.

A prospective observational study in Philadelphia between 1991 and 1994 explored the effect of ethnicity on macrosomia.²⁸ Macrosomia was defined as a BW >90th centile. Within the cohort, 103 American and 36 Latino subjects were followed prospectively. All subjects had been diagnosed with GDM. They found ethnicity is an independent risk factor for fetal macrosomia. However, ethnic variation in the United States is difficult to interpret as there is such wide ethnic intermingling.

The effect of parental height was extrapolated from the Millennium Cohort Study in the United Kingdom between 2000 and 2002.²⁹ There were 8053 infants studied. It showed maternal weight was more influential than paternal weight on infant BW.

Women with a history of fetal macrosomia are at risk of delivering another macrosomic infant. A retrospective study in Dublin between 1998 and 1999 reviewed 14,461 pregnancies.³⁰ From this cohort, 529 infants (3.7%) were macrosomic, with the incidence higher in parous women (4.6%) compared

Table 51.1 Risk factors of fetal macrosomia

Unmodifiable	Modifiable
Maternal age	Hyperglycemia
Parity	Hypertriglyceridemia
Ethnicity	Gestational age at birth
Parental height	Maternal weight
Gender of the fetus	Gestational weight gain
History of LGA infant	Dysfunctional lifestyle

with nulliparas (2.4%, $p < 0.0001$). In the following 5 years, 164 women went on to deliver a macrosomic fetus. They found that women with a history of one macrosomic fetus are at increased risk of another macrosomic fetus in a subsequent pregnancy (odds ratio [OR] 15.8, 95% confidence interval (CI) 11.45–21.9, $p < 0.001$). For women with two or more macrosomic fetuses, the risk is greater (OR 47.4, 95% CI 19.9–112.9, $p < 0.001$).

While all the previous factors are factored in, there are influences on BW that can be modified. These are of great interest to the clinician, for it is these that we can focus on in an effort to reduce the adverse maternal and fetal outcomes associated with the macrosomic infant. Modifiable risk factors may include maternal hyperglycemia, increased gestational age at delivery, increased maternal weight, increased gestational weight gain, and an unhealthy lifestyle.

The link between maternal and fetal hyperglycemia was first described in Copenhagen in 1952.³¹ Maternal hyperglycemia leads to fetal hyperglycemia as glucose crosses the placenta and insulin does not.³² Glucose is the main substrate for growth in the fetus.³³ In babies of mothers with diabetes, the effect of hyperglycemia is apparent as their BWs are increased. A prospective study in the northern region of the United Kingdom in 1994 enrolled 113 women with preexisting diabetes mellitus. The study found that 35% of those delivered (36 out of 104 deliveries) had a BW >95th centile.³⁴ In 2008, the HAPO study found that continuous exposure by the fetus to glucose, at levels below those diagnostic of diabetes, had a variety of adverse effects on the pregnancy including BW >90th centile.

Gestational age at delivery is an important risk factor for macrosomia. An observational study in California in 1997 studied the BW of 326 singleton fetuses born between 37 and 42 weeks gestation. They ensured the pregnancies were accurately dated and controlled for obesity, ethnicity, and lifestyle factors, e.g., smoking. The study found that BW was a linear function of gestational age between 37 and 42 weeks.³⁵ Despite this, however, studies have shown no benefit to induction of labor or cesarean section in nondiabetic mothers with suspected fetal macrosomia.²

Prediction

There has long been an interest in accurate methods or models for the prediction of fetal macrosomia. Clinical assessment has been the longest standing method. This involves subjective clinical palpation of the abdomen and measurement of the symphysiofundal height (SFH). These methods are fraught with inaccuracies as interobserver variation occurs. The measurement of SFH does not allow for variables such as polyhydramnios, uterine anomalies, or multiple pregnancies.³⁶

Some studies suggest that maternal prediction of macrosomia is accurate. A report in 1995 asked 70 postdate women to predict the fetal weight of their baby.³⁷ Among the cohort, the sensitivity was 56% and the specificity was 94%. The pre-test probability of macrosomia was taken to be 20%, and therefore, the post-test probability was 70%, comparable

to the accuracy of ultrasound estimation. However, this study considered those women in the general obstetric population. The accuracy of maternal estimates of BW among women with GDM has not been studied.

Ultrasound has been extensively studied for sensitivity and specificity in detecting fetal macrosomia. Twenty-two articles were reviewed in 2005.³⁶ The inclusion criteria were any study that considered the sensitivity and specificity of ultrasound-estimated fetal weight to correctly identify a macrosomic fetus. The authors considered macrosomia as fetal weight ≥ 4000 g. The majority of the reports that met the inclusion criteria were from the United States. Of the 22 reports, 14 were in the general obstetric population, 4 included pregnancies complicated by GDM, and 4 included postdate pregnancies.³⁶

The incidence of macrosomia among the general obstetric population (defined as BW >4000 g) ranged from 3% to 55%. The sensitivity and specificity in the detection of macrosomia in this group was wide ranging. The sensitivity ranged from 70% to 99%, while the specificity ranged from 12% to 79%. The time span of the articles included was 10 years (1993–2003). The review considered the possibility that a variation in the regression equation used by each study to predict BW influenced the results. Hadlock's proposed formula was used by 57% of the reports.³⁸ The post-test probability using this equation ranged from 17% to 76%. Of the 14 studies, 3 used the equation proposed by Shepard with a post-test probability ranging from 16% to 32%, and 1 study used various equations with a post-test probability ranging from 27% to 47%.³⁹ It concluded that the equation chosen was not a factor in the inconsistent results.

The review found that despite advances in equipment and expertise, our ability to predict the macrosomic infant has not improved over the decade. The expertise of the personnel conducting the ultrasound examination also does not influence the accuracy of prediction of fetal macrosomia.⁴⁰ A retrospective review in California recruited 365 women over a 7-month period. The prevalence of macrosomia (BW ≥ 4000 g) was 12%. The prediction of BW in the growth-restricted fetus and the appropriately grown fetus was more accurate among sonographers. However, both sonographers and fetomaternal specialists had similar accuracy in detecting the macrosomic fetus. The post-test probability to detect the macrosomic fetus was 53% and 56%, respectively.

The ability to predict macrosomia in the general obstetric population is fraught with inaccuracy. However, evidence suggests it is feasible to predict macrosomia in pregnancies complicated by diabetes mellitus and in postdate pregnancies. It is most likely that the reason for greater detection is the higher prevalence of macrosomia among these groups. The post-test probability of detection of a macrosomic fetus ranged from 71% to 81% in those with GDM and 61%–63% in postdate pregnancies.^{41–44} These studies defined macrosomia as ≥ 4000 g.

Neonatal morbidity due to birth trauma is more likely to occur when the BW is ≥ 4500 g.⁸ Therefore, it is prudent to consider if macrosomia can be predicted—either clinically or sonographically—in this select group of patients. In the

literature, reviews suggest a post-test probability of detection of macrosomia in infants ≥ 4500 g varies from 22% to 37% on ultrasound and 12% to 36% on clinical examination.^{2,45–47} Present evidence indicates that it remains difficult to predict infants who weigh ≥ 4500 g either clinically or on ultrasound.

Serum biomarkers that are sensitive and specific could potentially predict fetal macrosomia. This area remains in its infancy, and the results to date show only a relatively small improvement in overall prediction of macrosomia.⁴⁸ Low pregnancy-associated plasma protein A and increased beta human chorionic gonadotropin levels have been shown to be predictive in pregnancies complicated by growth restriction. However, the reverse has not been proven true when it comes to the prediction of macrosomia. The use of biomarkers for predicting macrosomia, from as early as the first trimester, has been investigated but with only marginal increase in detection.⁴⁸ These markers were used in combination with maternal risk profile.

Prevention

The root of macrosomia is multifactorial. Therefore, there are many aspects that can be considered when it comes to preventing this obstetric challenge.

The effect of maternal hyperglycemia on fetal macrosomia is established. Glucose crosses the placenta, while insulin does not. This results in fetal hyperglycemia and a subsequent hyperinsulinemia and fetal macrosomia.⁴⁹ In a pregnancy complicated by diabetes, there is central deposition of subcutaneous fat in the abdominal and interscapular areas. However, the skeletal growth is unaffected.⁵⁰ A prospective study of 479 healthy, nondiabetic mother and baby pairs concluded that the effect of maternal hyperglycemia on fetal growth is mainly related to fat deposition.³⁰ Therefore, it stands to reason that control of hyperglycemia is essential to prevent macrosomia. There is some evidence also that altering the carbohydrate type consumed from high to low glycemic index changes glucose and insulin response, in turn altering fetal weight gain.⁵¹

The impact of maternal obesity on fetal BW may be a factor to be considered in preventing macrosomia. A retrospective observational study in Cleveland reviewed 12,950 deliveries from 1997 to 2001 to evaluate whether an abnormal body habitus contributed to the birth of a macrosomic infant.⁵² The subjects were classified as underweight, normal, overweight, or obese (defined as >30 kg/m²). Obesity was not further classified into subgroups. Macrosomia was defined as BW >90 th centile. They concluded that obese women had an increased risk of macrosomia (16.8% vs. 10.5%, $p < 0.001$) as were overweight women (12.3% vs. 10.5%, $p < 0.01$). The rate of abnormal body habitus is steadily rising, particularly in the obesity classes. This may impact on the rate of macrosomia and, in doing so, will increase the morbidity associated with macrosomia for both mother and baby. There are also uncertainties about whether any epidemiological associations between obesity and macrosomia may be genetic or may be due to concomitant GDM. Ideally, it is prepregnancy or interpregnancy weight gain that we should be aiming

to reduce and also weight gain in the current pregnancy, if BMI is to be optimized.

Maternal obesity may influence fetal macrosomia. However, possibly of more importance is the concept of maternal body composition. Considering the overall body composition and not just BMI may be a more appropriate focus for both the prediction and prevention of fetal macrosomia. In a prospective observational study, our research team studied the correlation between fetal BW and maternal body composition.⁵³ The study included 2618 subjects of whom 16.5% were obese. We concluded there was no relationship between maternal fat mass and fetal macrosomia. However, fat-free mass was a strong predictor of BW ≥ 4.0 kg. Women who were in the highest fat-free mass quartile had an odds ratio of 3.6 for a BW >4000 g compared to those in the lowest quartile (Figure 51.5).

The impact of body composition on BW is further demonstrated by work carried out in our unit. This prospective study recruited 368 women across all BMI categories. The BW of babies was recorded and compared against maternal body composition. This shows the range of fetal BW across all BMI categories.

Obstetric interventions are made in a bid to reduce the incidence and impact of fetal macrosomia. It has previously been postulated that elective cesarean section or induction of labor may avoid the adverse outcomes of macrosomia. However, neither approach has shown clear benefit in women with otherwise uncomplicated pregnancies.

A retrospective analysis in 1983 reviewed the outcomes for infants with a BW > 4000 g.⁵⁴ They concluded that macrosomia was rare at 37 weeks gestation and increasingly more common thereafter. They advocated ultrasound analysis between 36 and 38 weeks gestation and subsequent induction of labor for suspected macrosomia.

It must also be considered that induction of labor in itself increases the rate of cesarean section. Eleven studies, both observational and randomized, which compared expectant

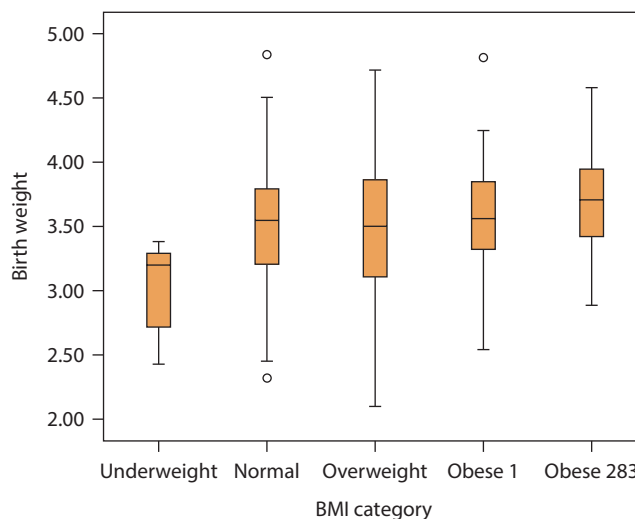


Figure 51.5 The relationship between BMI and birth weight. (From Higgins, O. et al., *Ir. Med. J.*, 107, 10, November 2014. With permission.)

management versus induction of labor when fetal macrosomia was suspected were reviewed.⁵⁵ These 11 studies included 3751 subjects of which 2700 were managed expectantly and 1051 underwent labor induction. Analysis showed that, compared with those whose labor was induced, women who experienced spontaneous onset of labor had a lower incidence of cesarean section (OR 0.39, 95% CI 0.30, 0.50) and higher rates of spontaneous vaginal delivery (OR 2.07, 95% CI 1.34, 3.19). No differences were noted in rates of operative vaginal delivery, shoulder dystocia, or abnormal Apgar scores in the analyses of the observational or randomized studies.⁵⁵

Pregnancy complicated by GDM is an independent risk factor for neonatal morbidity. Shoulder dystocia was more common in diabetic women.⁵⁶ Within this study, it was concluded that the combination of diabetes and a macrosomic infant, with macrosomia defined as ≥ 4000 g, accounted for 73% of shoulder dystocia cases among women with GDM. Therefore, it was concluded that cesarean section was indicated in those with GDM and an estimated fetal weight ≥ 4000 g.⁵⁶ A similar increased risk of brachial plexus injury associated with GDM has also been demonstrated.⁵⁷

The complications associated with macrosomia in those with GDM are recognized and cesarean delivery in these cases has been widely recommended.^{56–58} However, the cutoff value at which cesarean section is advised remains

contentious. Some advise a cutoff value of >4000 g, others advise >4250 g, and the ACOG recommends >5000 g.^{56,58,59} It remains reasonable that cesarean section should be discussed in the context of GDM and suspected fetal macrosomia >4500 g.

Conclusion

Macrosomia remains a contentious and controversial topic in obstetric practice. There is little doubt that a pregnancy complicated by macrosomia leads to a greater risk of maternal and neonatal morbidity. It is, therefore, a pregnancy complication that we strive to both predict and prevent. However, the effects are wide reaching. Our prediction tools at present are ineffective.

The suspicion of macrosomia heightens both maternal and clinician anxiety and often leads to more investigation and more intervention than in the pregnancy where fetal growth is considered to be normal. The challenges facing us when it comes to macrosomia are wide ranging. It is hoped that through greater research and an agreed definition of macrosomia, the tools for prediction and the strategies for prevention will become more precise and widely used among clinicians worldwide.

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52 Hypoglycemia in diabetic pregnancy

Graziano Di Cianni, Cristina Lencioni, Emilia Lacaria, and Laura Russo

Introduction

Hypoglycemia is a major factor preventing patients with both type 1 and type 2 diabetes from achieving near-normal glycemia. The risk of hypoglycemia in diabetic patients is due to both the imperfect pharmacokinetics of current therapy that produces inappropriately high insulin concentrations and a failure in the physiological protective mechanism that limits the decrease in blood glucose concentrations. Hypoglycemia occurs as a result of good metabolic control and is a limiting factor in achieving the highest possible value in the daily glycemic profile, in every condition in which it is required.

Maternal blood glucose control in pregnancy, as close to that of normal pregnancy, is essential in minimizing the negative effects on the mother and the fetus. Strategies to achieve and maintain normal glycemia in pregnancy are onerous but not negotiable, and hypoglycemia becomes nearly inevitable using available strategies. In addition, pregnancy itself may be associated with impaired counterregulation system and hypoglycemia unawareness. This could result in an increase of severe hypoglycemic episodes.

The incidence, risk factors, and possible pathophysiological factors of maternal hypoglycemia, its effects on the mother and on the fetus, and the management of hypoglycemia during pregnancy are discussed in detail in this chapter.

Hypoglycemia in diabetes

Hypoglycemia is the most frequent acute complication of type 1 diabetes mellitus therapy. It has been reported that diabetic people live about 10% of their lives with glycemic values lower than 50 mg/dL (2.8 mmol/L) and that on average once a week they present an episode of symptomatic hypoglycemia and one episode of severe hypoglycemia per year.^{1,2} About every 4–5 years, a case of this can lead to coma with the need of assistance and admission to hospital.³ In 2%–4% of the cases, hypoglycemia causes death for people with type 1 diabetes mellitus.⁴

Hypoglycemia is a common complication also for people with type 2 diabetes. The rate of severe hypoglycemia in type 2 diabetes is roughly one-third to that of

type 1 diabetes. Nevertheless, the prevalence rates rise up to 70%–80% in clinical trials using insulin to achieve good metabolic control.⁵

Symptoms

A single threshold value for plasma glucose concentration that defines hypoglycemia in diabetes cannot be assigned. In fact, glycemic threshold for symptoms of hypoglycemia shift from lower plasma glucose concentration in patients with more frequent episodes of hypoglycemia to higher plasma glucose concentrations in those with poorly controlled diabetes. However, hypoglycemia in diabetes usually has a plasma glucose concentration below 70 mg/dL (3.9 mmol/L).⁶

Symptoms of hypoglycemia, which are the same also during pregnancy, are divided into two categories: neurogenic and neuroglycopenic (Figure 52.1). Neurogenic (autonomic) symptoms, activated by the autonomic nervous system and mediated by norepinephrine, epinephrine, and acetylcholine, include anxiety, palpitations, sweating, shakiness, dry mouth, pallor, pupil dilatation, diaphoresis, hunger, and paresthesia.

The insufficient contribution of glucose to the brain (neuroglycopenia) with an associated cerebral reduction of oxygen causes neuroglycopenic symptoms. The cognitive function becomes impaired when plasma glucose concentration falls below 50–55 mg/dL (2.7–3 mmol/L).⁷ These symptoms include abnormal mentation, irritability, difficult speaking, ataxia, paresthesia, headache, stupor, and eventually (if untreated) seizure, coma, and even death. Neuroglycopenic symptoms also include transient focal neurological deficits (e.g., diplopia, hemiparesis). These symptoms usually represent the alarm signal of a more serious hypoglycemic attack, and they usually precede the alterations of the cortical function. In this phase, the person is completely vigilant, but he/she can completely prevent the attack from occurring by consuming foods rich in fast-absorbing carbohydrates.

Severe hypoglycemia appears when glucose levels continue to decrease. In this case, the person is incapable of starting a treatment for the resolution of the episode and he or she needs a rapid and adequate assistance.

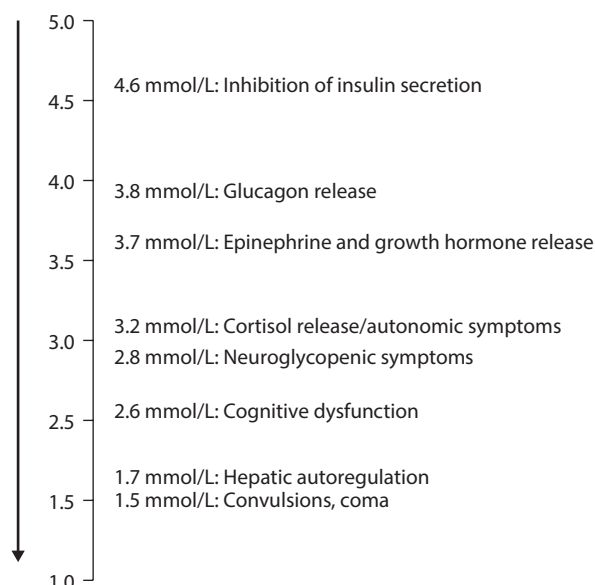


Figure 52.1 Symptoms of hypoglycemia.

Pathophysiology

Glucose, in physiological conditions, provides 90% of the energy necessary for brain functioning, and the cerebral functions are totally dependent on the level of the circulating glucose. The decrease of the glycemic values results in a series of redundant neuroendocrine responses, aiming to bring the glycemic levels to the physiological range⁸ (Figure 52.2).

Decreasing plasma glucose concentrations are sensed in the hypothalamus and other regions of the brain as well as in the hepatic portal vein and the carotid body. Glucose sensing in visceral sites send their information to the brain via the cranial nerve (especially the vagus nerve), and as a

result of a complex integration within the brain, these signals are responsible for the autonomic response (sympathetic and parasympathetic) organized within the hypothalamus.⁹ Glycemic reduction in the physiological area (about 4.4 mmol/L) causes a decline in insulin secretion that results in an increased production of glucose from the liver. This represents the initial defense against decreasing glucose levels.¹⁰

Glucagon stimulates hepatic glycogenolysis and it also favors gluconeogenesis, but it also seems to determine autonomic inputs. Epinephrine has a similar action to that of glucagon, but it becomes of critical importance when there is insufficient glucagon secretion. These two hormones are therefore considered the ones mainly involved in the counterregulation response; in fact, the development or the accentuation of the hypoglycemic crisis does not take place without these two hormones.

Other hormones, however, such as the growth hormone and cortisol, are involved in counterregulation, especially in prolonged hypoglycemia. Their effects are carried on by limiting the glucose consumption and by favoring their production.¹¹

The defense mechanisms against hypoglycemia are clearly impaired in patients with type 1 diabetes and advanced type 2 diabetes, which became unable to decrease insulin levels and to increase glucagon levels in response to hypoglycemia. The loss of β -cell function determines that insulin circulating levels are only a function of exogenous insulin clearance and there is a reduced signaling of functional alpha cells to secrete glucagon as glucose concentration levels decrease. Under these conditions, epinephrine remains critical for counterregulation because the two physiological defense mechanisms against hypoglycemia are impaired.⁷ However, many patients with type 1 diabetes, especially after recurrent hypoglycemia and in the presence of extended

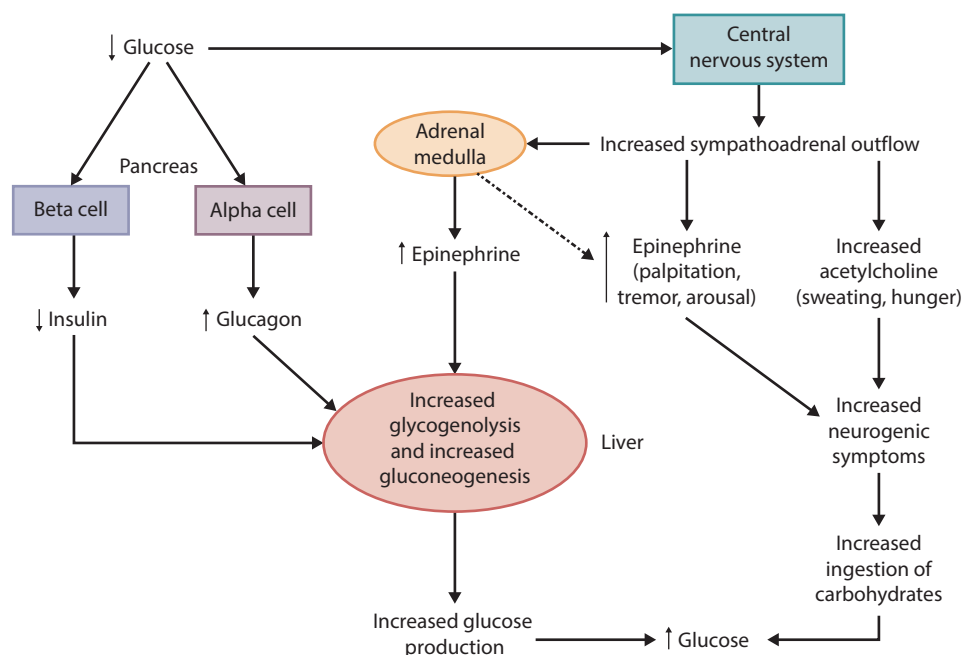


Figure 52.2 Physiological mechanism against hypoglycemia. The decreased in glucose concentration in blood includes a decreased in insulin secretion, an increase in glucagon secretion, and an increase in epinephrine secretion.

duration diabetes (10–20 years), suffer from reduced responses of epinephrine. Therefore, patients with type 1 diabetes with combined defect of glucagon and epinephrine are at about sixfold increased risk for severe iatrogenic hypoglycemia during intensive insulin therapy.¹²

Hyperinsulinemia is the rule in diabetes mellitus, both type 1 and type 2, because of the therapeutic delivery of insulin into the peripheral rather than portal circulation and because of the empirical algorithms used to administer insulin. Absolute hyperinsulinemia, due to excessive levels of circulating insulin (excess of dosage or irregularity of absorption), causes hypoglycemia more frequently during the hours preceding meals or in the first hours in the morning. Relative hyperinsulinemia, due to other conditions such as delayed or inadequate diet (especially as far as the range of carbohydrates is concerned), physical exercise, renal failure, excessive alcohol consumption, and delayed gastric emptying, usually causes hypoglycemia after meals.¹³

Type 2 diabetes is characterized by insulin resistance and persistent beta cell function, which allows insulin secretion to decrease as blood glucose decreases, and apparently intact counterregulation. Consequently, as reported in the literature,⁹ the rate of severe hypoglycemia results is lower than in type 1 diabetes. However, the United Kingdom Prospective Diabetes Study (UKPDS) showed that the frequency of hypoglycemia increases over the years with a prolonged duration of insulin treatment.¹⁴ Patients with advanced type 2 diabetes and long duration of insulin treatment have reduced both glucagon and sympathoadrenal response to hypoglycemia.⁹

In people with type 2 diabetes, hypoglycemia is often a consequence of the pharmacological treatments with hypoglycemic agents that stimulate pancreatic insulin secretion (sulfonylureas, glinides).

Hypoglycemia unawareness

Hypoglycemia unawareness is a common long-term complication of diabetes. Recent evidences suggest that 10%–15% of individuals with type 1 diabetes mellitus exhibit hypoglycemia unawareness, whereas impaired awareness (patients who usually, but not always, experience symptoms of hypoglycemia during hypoglycemic episodes) is seen in 40%–50%.^{1,15} In insulin-treated type 2 diabetes mellitus, hypoglycemia unawareness has been reported to be approximately 10%.¹⁶

The exact mechanism of hypoglycemia unawareness is not completely understood.

It is thought to be due to an alteration in the relationship between glycemic thresholds of the various components of the physiological response to hypoglycemia and cognitive functions.¹⁷ Patients with hypoglycemia unawareness demonstrate sympathoadrenal activation at lower glucose concentrations than those who have awareness and, importantly, at a lower level than that for cognitive impairment.

Strong evidence indicates that defective loss of symptoms of hypoglycemia in patients with type 1 diabetes is largely the result of antecedent, frequent hypoglycemia. It seems likely that antecedent hypoglycemic episodes contribute to defective glucagon response and impaired secretion of

epinephrine during hypoglycemia. The attenuated epinephrine response to hypoglycemia is a marker of an attenuated autonomic and sympathetic response.⁷ It causes the initial loss of the warning symptoms of hypoglycemia and, over time, through a downward vicious spiral including progressively impaired physiological responses and increasing clusters of hypoglycemic episodes, the development of hypoglycemia unawareness.¹⁸

Cardiovascular, cognitive impact, and mortality associated with hypoglycemia

Severe and prolonged hypoglycemia can cause death: recent studies have demonstrated that up to 10% of patients with type 1 and sulfonylurea-treated type 2 diabetes mellitus died of hypoglycemia. Potential mechanisms include brain death and cardiac arrhythmias (including torsade de pointes and atrial fibrillation).¹⁹

Acute prolonged hypoglycemia causes a marked increase in the workload of the heart, compromises endothelial function, and increases blood coagulability and viscosity.²⁰

A recent retrospective study reported a 79% higher risk in cardiovascular events compared to patients without hypoglycemic events in patients with type 2 diabetes.²¹ Three large trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD),²² Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE),²³ and Veterans Affairs Diabetes Trial (VADT),²⁴ examined the effects of glucose lowering the cardiovascular events in patients with type 2 diabetes: a total of 24,000 patients with high cardiovascular risk were assigned to either intensive control or standard therapy. Subjects assigned to the intensive arm experienced more episodes of hypoglycemia than those randomly assigned to standard treatment arm. In the ACCORD trial, subjects assigned to more intensive treatment also experienced a 20% increase in mortality. In contrast in the ADVANCE or VADT study, recent severe hypoglycemia was a strong predictor of negative cardiovascular outcome. The results are still conflicting and a matter of debate.

Data from a mean 18 years of follow-up in the Diabetes Control and Complications Trial (DCCT) show no association between hypoglycemia and a decline in any cognitive domain.²⁵ Recent findings show that adults with type 1 diabetes require a greater volume of the brain to perform a working memory task during hypoglycemia.²⁶

In type 2 diabetes mellitus, current evidence suggests that recurrent hypoglycemia does not cause cognitive impairment in young middle-aged patients. Data are conflicting regarding the impact of severe hypoglycemia on the risk of dementia among elderly patients with type 2 diabetes mellitus.^{27,28}

Hypoglycemia in diabetic pregnancy

In pregnant women with diabetes (type 1 and type 2), a good metabolic control before and during pregnancy is essential to reduce the maternal–fetal morbidity and mortality.²⁹ This

is true for women with pregestational type 1 or type 2 diabetes as well as for those with gestational diabetes mellitus. To obtain and maintain an optimal daily glycemic profile and HbA1c levels to near-normal values during pregnancy, women with diabetes are at increased risk of severe hypoglycemic episodes. Moreover, in nondiabetic pregnancy, normal blood glucose levels are 20% lower than in nonpregnant women,^{30,31} making the definition and the detection of hypoglycemia more challenging.

Around 45%–71%^{32–34} of women with type 1 diabetes experienced severe hypoglycemia during pregnancy. Furthermore, in front of similar glycemic control, almost 60% of severe hypoglycemic episodes are experienced by only 10% of pregnant women with type 1 diabetes.³⁵

Severe hypoglycemia occurs three to five times more frequently in the first trimester and at a lower rate in the third trimester.³⁵ This is despite the fact that, in the third trimester, a more stringent metabolic control is followed by the majority of women by administering much higher insulin doses as compared with early pregnancy. The first event usually occurs before 20 weeks, and 80% of all events are recorded before 20 weeks³² (Figure 52.3).

Despite the higher incidence of severe hypoglycemia in pregnancy, the proportion of nocturnal severe hypoglycemia events is similar before and during pregnancy and at a similar level to that reported in the DCCT among nonpregnant patients with type 1 diabetes.³⁶ A pre-bedtime glucose value below 6.0 mmol/L predicts nocturnal biochemical hypoglycemia in the first trimester among pregnant women with type 1 diabetes.³⁵ Interestingly, the vast majority of these hypoglycemia episodes are asymptomatic, suggesting that the nocturnal severe hypoglycemia events recorded by patients only represent the tip of the iceberg of all nocturnal hypoglycemic periods. Nocturnal asymptomatic hypoglycemia may be associated with the development of hypoglycemia unawareness.³⁷

Pathophysiology

Impairment of glucose counterregulation

Diabetic pregnancy is characterized per se by an impairment of the counterregulatory response. As observed by experimental studies performed in diabetic dogs, epinephrine and glucagon responses to hypoglycemia result in an impaired glucose counterregulation during pregnancy.³⁸ Moreover, these data have also been confirmed in human pregnancy by using the hypoglycemic clamp technique.^{16,39}

In pregnant women with intensively treated type 1 diabetes, consistent lower epinephrine and glucagon responses were found with respect to nondiabetic nonpregnant women. In addition, the glycemic thresholds for epinephrine and growth hormone secretion decreased. This may be the consequence, at least in part, of the intensive insulin treatment of the patients. An impairment of secretion of both hormones, especially that of glucagon, has also been demonstrated in nondiabetic pregnant women. The exact mechanisms involved in the reduction of glucagon and epinephrine secretion during pregnancy are not completely clear. Nevertheless, as for glucagon, one possibility is that the placental hormones exert a suppressive effect on it. In this context, it has been reported that the arginine-induced secretion of glucagon is decreased in women using hormonal contraception.¹⁶ These data imply a suppression of these hormones by the high levels of estrogen and progesterone that characterize pregnancy. Moreover, the results of a more recent experimental study suggest that the blunting of glucagon secretion during insulin-induced hypoglycemia in pregnancy is related to a generalized impairment of a number of different signals, including parasympathetic and sympathoadrenal stimuli and altered sensing of circulating and/or intraislet insulin.⁴⁰

Also, growth hormone response during pregnancy is progressively reduced in pregnant women both with and without diabetes, and this can be determined by the progressive

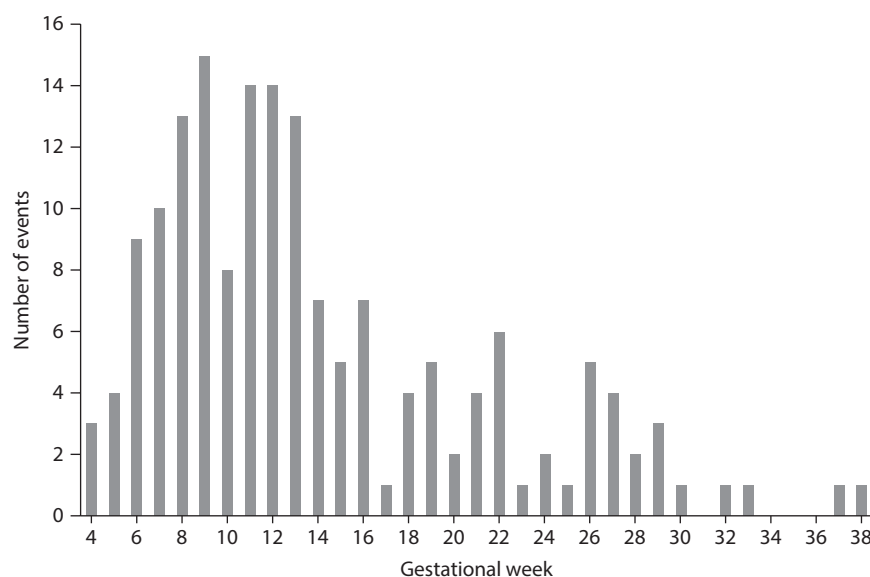


Figure 52.3 Rate of severe hypoglycemic events per week during pregnancy in 108 women with type 1 diabetes. (Modified from Ringholm, L. et al., *Diabet. Med.*, 29, 558, 2012.)

increase of placental hormones.¹⁶ Another study using hyperinsulinemic hypoglycemic clamp in pregnant women with type 1 diabetes in the third trimester of pregnancy showed a significant increase of placental growth hormone during hypoglycemia. These observations indicate that the placenta is an endocrine organ that can play an active role in acute metabolic processes such as the hormonal counterregulation of hypoglycemia.⁴¹ In fact, placental growth hormone has well-established hyperglycemic and insulin-antagonistic properties and may exert its glycemic effects directly or indirectly by insulin-like growth factor-I (IGF-I).^{42–44} More recent studies showed that, in normal pregnancy, maternal placental growth hormone levels increase and gradually replace the pulsatile pituitary growth hormone production⁴⁵; moreover, from 20 weeks, pituitary growth hormone levels decrease and remain at minimal levels in the third trimester.⁴⁴

In pregnant women with type 1 diabetes, low IGF-I levels are present in the first half of pregnancy and tend to increase until late pregnancy.^{43,46} In particular, women with type 1 diabetes experiencing repeated severe hypoglycemia during pregnancy showed lower IGF-I levels as compared with women without repeated severe hypoglycemia.⁴⁶ Thus, the additive influence of pituitary growth hormone and placental growth hormone on peripheral metabolism may be at its lowest in early pregnancy where the incidence of severe hypoglycemia is highest.

Pregnancy induces substantial changes in the renin-angiotensin system. During the early stages of pregnancy, activation of the local and systemic renin-angiotensin system has been demonstrated and may be important for implantation and embryonic growth and development. Angiotensin-converting enzyme activity may be higher in pregnant women with type 1 diabetes compared with healthy pregnant women. However, only a weak association between angiotensin-converting enzyme activity and severe hypoglycemia has been detected during pregnancy.^{35,47}

Risk factors

Hypoglycemia during diabetic pregnancy is certainly linked to the intensified insulin treatment useful to reach and maintain the targets of glycemic control recommended in these pregnant women. Moreover, the impairment of glucose counterregulation^{42,48} and other features such as an increase in insulin sensitivity during the first trimester of gestation⁴⁹ are important in determining an increase in hypoglycemic episodes during pregnancy. Diabetic pregnancies are often characterized by hypoglycemia unawareness; the mechanisms operating during pregnancy are not different from those outside pregnancy. In particular, the exposure to low blood glucose levels requested to obtain an ideal daily glycemic profile is the main factor involved in the reduced hypoglycemia awareness in pregnancy. Risk factors for severe hypoglycemia in pregnancy include a history of severe hypoglycemia in the preceding years, long duration of diabetes, low HbA1c in early pregnancy, fluctuating plasma glucose levels, and excessive use of supplementary insulin between meals and impaired hypoglycemia awareness.

Table 52.1 Risk factors for severe hypoglycemia in pregnant diabetic women

History of severe hypoglycemia in the preceding year
Long duration of diabetes
Impaired hypoglycemia awareness
Low HbA1c in early pregnancy
Fluctuating plasma glucose levels
Excessive use of supplementary insulin between meals
Nausea and vomiting

Finally, nausea and vomiting, common in the first trimester, may contribute to hypoglycemia by reducing the ingestion of carbohydrate (Table 52.1).

Symptoms

According to the entity of the clinical presentation, both in pregnancy and outside pregnancy, hypoglycemia can be classified as severe (an event requiring assistance of another person) documented symptomatic hypoglycemia (an event with typical symptoms that are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL), asymptomatic hypoglycemia (an event not accompanied by typical symptoms but with a measured plasma glucose concentration ≤ 70 mg/dL), probable symptomatic hypoglycemia (an event with typical symptoms not accompanied by a plasma glucose concentration), and pseudohypoglycemia (an event with typical symptoms of hypoglycemia with a measured plasma glucose concentrations >70 mg/dL).

Fetal consequences

A series of experimental studies in animals have demonstrated a teratogenic effect of maternal hypoglycemia occurring during the embryogenesis. The exposure, in vitro, of mouse embryos to hypoglycemic milieu even for short periods (2 hours) in the first stages of embryogenesis resulted in malformations. This could be explained by the fact that younger embryos are very sensitive to hypoglycemia because they are dependent on uninterrupted glycolysis and have not yet developed the ability for aerobic glucose metabolism.^{50,51}

Studies regarding a potential teratogenic effect of hypoglycemia in pregnant women are few. Impastato et al.,⁵² more than 40 years ago, reported that 6 out of 19 normal pregnant women who received insulin coma therapy, for psychiatric disorders, during the early phase of pregnancy, had malformed fetus. The following clinical studies evaluating the potential teratogenic effect of maternal hypoglycemia in diabetic patients, as reported in Table 52.2, showed no increase in the frequency of fetal malformations in women who experienced frequent episodes of hypoglycemia.^{35,52–64}

However, due to the limited data reported in literature and to the fact that no prospective studies have been performed on this topic, the possibility that severe episodes of hypoglycemia may contribute to congenital malformations cannot be completely excluded.

Table 52.2 Maternal hypoglycemia and embryogenesis in pregnancies with type 1 diabetes

Study author	Time of exposure glycemic levels	Pregnancy outcome
Impastato ⁵²	<10 gestational week (gw) (19 nondiabetic women)	Abortion, ² stillbirth, ² multiple malformations, ¹ Hirschsprung's disease ¹
Molsted-Pedersen ⁵³	First trimester	Lower frequency of maternal hypoglycemia in malformed infants
Bergman ⁵⁴	Whole pregnancy (BG < 3.3mmol/L)	No relationship with malformations
Rayburn ⁵⁵	Whole pregnancy (altered consciousness requiring assistance by another person)	No relationship with malformations
Mills ⁵⁶	5–12 gw BG < 2.8 mmol/L or symptoms	No relationship with malformations
Steel ⁵⁷	<9 gw Severe hypoglycemia	No relationship with malformations
Kitzmiller ⁵⁸	2–8 gw BG < 2.7 mmol/L or symptoms	No relationship with malformations
Kimmerle ³⁵	Not known Hypoglycemic coma	No relationship with malformations
Rosenn ⁵⁹	7–13 gw Severe hypoglycemia	No relationship with malformations
DCCT ⁶⁰	First trimester Severe hypoglycemia	No relationship with malformations
Palomar-Morales ⁶¹	Whole pregnancy	No relationship with malformation
Taylor ⁶²	Whole pregnancy	No relationship with malformation
Mitanech ⁶³	Whole pregnancy	No relationship with malformation
Talaviya et al. ⁶⁴	Whole pregnancy	No relationship with malformation

Abbreviation: BG, blood glucose.

Studies aimed to evaluate fetal heart rate (FHR) during hypoglycemia in diabetic pregnant women are conflicting. While some studies showed fetal tachycardia during maternal hypoglycemic coma,⁶⁵ others showed bradycardia and reduced fetal movements during maternal hypoglycemia.⁶⁶ An increased FHR has been demonstrated during hypoglycemic clamp studies, probably as a consequence of maternal increased sympathetic adrenal activity.⁶⁷ On the contrary, other studies have reported no changes in FHR and fetal movements, suggesting that the fetus could use alternative substrate during episodes of maternal hypoglycemia.⁶⁸ With correction of maternal blood glucose levels, FHR and fetal activity returned to normal.

Although data regarding congenital malformations and functional cardiac anomalies are not conclusive, it is accepted that low levels of maternal glucose during pregnancy may cause fetal growth retardation and small-for-gestational-age infants.

Langer has shown that in gestational diabetic pregnant women, the frequency of small-for-gestational-age infants was 20% in women with low mean plasma glucose levels (<4.8 mmol/L), significantly higher with respect to normal pregnant women (11%).⁶⁹

In addition, maternal hypoglycemia may also determine impaired fetal beta cell function. In fact, animal experimental studies suggest that fetus with intrauterine growth restriction caused by chronic placental insufficiency have impaired insulin secretion, insulin biosynthesis, and insulin content. The fetal beta cell dysfunction might indicate mechanisms

that are developmentally adaptive for fetal survival, but later in life might predispose offspring to adult-onset diabetes.⁷⁰

The degree of glycemic control during pregnancy affects perinatal outcome; nevertheless, data of pregnancy outcome in diabetic women with repeated hypoglycemia are few. Perinatal outcome seems not to be affected by severe episodes of hypoglycemia.^{35,54} Finally, studies in children of mothers who experienced frequent severe hypoglycemic episodes during pregnancy showed no relation between intellectual performance, psychomotor development, and hypoglycemia. Rizzo et al. studied children of mothers with hypoglycemia during the second and third trimester of pregnancy. They found normal intelligence scores at 2 and 5 years of age.⁷¹ Maternal hypoglycemia in the first or third trimester has not been shown to predict cognitive function in adult offspring of women with type 1 diabetes.⁷²

Treatment

Diabetic people should be educated to identify correctly the alarm symptoms of hypoglycemia and to treat themselves promptly to prevent progression to neuroglycopenia. All hypoglycemic episodes, even in the absence of symptoms, require treatment. The goal of the treatment is to increase the blood glucose to a safe level to avoid clinical consequences.

Relatives, friends, teachers, and coworkers should be taught to recognize symptoms of hypoglycemia, and in case

of doubt, they must treat immediately the person that may have hypoglycemia.

Mild to moderate hypoglycemia is usually treated with food, oral glucose tablets, or sucrose solutions. It is sufficient to administer 15–20 g of glucose as glucose tablets (3–5 g/10 kg body weight) or sports drinks containing pure glucose to raise blood glucose by 65 mg/dL (3 mmol/L). Fruit juice is absorbed more slowly than glucose and is not as effective in raising the blood glucose levels as tablets or liquid glucose. Likewise, honey is less efficient than glucose because it contains only 40%–50% glucose and the same amount of fructose. Sucrose solution as granulated sugar in orange juice or milk does not provide a quick rise in blood glucose levels for rapid symptomatic relief and may require the administration of a larger volume.

Moderate hypoglycemia may require a second administration of glucose.

In case of loss of consciousness, the treatment is 10–25 g (20–50 mL of 33% glucose solution injected intravenously over 1–3 minutes). The intravenous infusion of glucose solutions (20–50 mL at 33%) is the advised treatment for the hospitalized patient.

The administration of glucose solutions at 33% must be carefully controlled to avoid phlebitis and pain in case of breaking of the vein.

Glucagon is ideal to use at home and the standard dose is 1 mg given subcutaneously. The maximal blood glucose response occurs after 15 minutes, with a peak at 20 minutes to 1 hour. When glucagon is used, it is important to remember that postglucagon nausea and vomiting are common and that careful monitoring of blood glucose levels should be continued until the patient is able to eat normally.

Glucagon does not cross the placenta and its use in pregnancy is not dangerous.⁵⁸

Effective approaches known to decrease the risk of iatrogenic hypoglycemia include patient education, dietary and exercise modifications, medication adjustment, careful glucose monitoring by the patient, and conscientious surveillance by the clinician.⁶

Optimizing insulin therapy is essential to reduce the risk of hypoglycemia in diabetic pregnant women; the use of both short- and long-acting insulin analogues during pregnancy can reduce the risk of severe hypoglycemia.^{73–75} The data that insulin pumps can help with the reduction of severe hypoglycemia during pregnancy are not well established.⁷⁶ A case report suggested that insulin pump therapy combined with real-time continuous glucose monitoring, with careful monitoring of glucose values, is useful in preventing severe hypoglycemia in pregnant women with impaired hypoglycemia awareness.^{35,77}

Conclusions

Diabetic pregnancy represents the most important challenge of insulin therapy, requiring a continuous effort to maintain euglycemia and avoid severe hypoglycemic episodes. The frequent exposure to low glucose levels determines an impaired glucose counterregulation and hypoglycemia unawareness. Hypoglycemia may be dangerous for the mother, but it is unclear whether and to which extent it determines embryopathy. Finally, the worry about hypoglycemic episodes can have a negative impact on the experience of pregnancy for the mother and her partner. Women should avoid hypoglycemic episodes and be able to prevent them. Therefore, women have to be adequately instructed to perform self-monitoring of blood glucose and observe the diet especially of the intermeal snacks and insulin plan. The new technology for monitoring the glucose profile daily will be a useful tool to reduce *hypoglycemic episodes in pregnancy with diabetes* in the next years.

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53 Hypertensive disorders and diabetic pregnancy

Jacob Bar, Moshe Hod, and Michal Kovo

Metabolic syndrome: When hypertension and diabetes meet

The striking increase in the prevalence of obesity, diabetes mellitus (DM), hypertension, and cardiovascular disease in the last two decades¹ has led to the concept of the metabolic syndrome.² Also termed syndrome X,³ insulin resistance syndrome,⁴ and the deadly quartet,⁵ metabolic syndrome is characterized by a constellation of well-documented risk factors for cardiovascular disease, namely, glucose intolerance, insulin resistance, central obesity, dyslipidemia, and hypertension, that co-occur in individuals at a higher rate than expected by chance. Extensive research has still not completely elucidated the precise cause of the syndrome, although some strong positions have been taken. Nevertheless, it is widely recognized that a combination of genetic predisposition and environmental factors, particularly those associated with socioeconomic status, is involved. The environmental factors include both postnatal life habits and nutrition and—no less important—intrauterine conditions. Indeed, there is plentiful evidence linking low birth weight due to fetal growth restriction (FGR) with an increased risk of vascular disease in later adult life.⁶

Intrauterine factors in metabolic syndrome: The fetal origin of adult disease

Barker⁶ pioneered the idea that the epidemic of coronary heart disease in Western countries in the twentieth century, which paradoxically coincided with improved standards of living and nutrition, originated in fetal life. He postulated that the low birth weight and impaired fetal growth that were characteristic of deprived regions in the 1900s may have predisposed the survivors to heart disease in later life. Support was provided by studies conducted in Hertfordshire, England, showing a higher rate of cardiovascular mortality in men who had been small at birth and at 1 year of age.⁶ Thereafter, at least seven retrospective cohort

studies reported an association of low birth weight with high risk of later ischemic heart disease^{7–12} and stroke^{13,14} or impaired glucose tolerance and DM.^{15,16} It was also found to be associated with high blood pressure (BP) in childhood^{17,18} and adult life.¹⁹ The evidence was strongest for BP and glucose tolerance,²⁰ which could be measured earlier in life and for which more data, and sometimes also prospective data, were available.^{19,21} The evidence was weaker, though still convincing for heart disease, for which data were sparse and often confined to men. The findings in the few studies on stroke, particularly the hemorrhagic type, were consistent.¹⁴

In another study, Barker et al.²² observed that the effects of impaired fetal growth are modified by subsequent growth. As such, individuals who were small at birth but became overweight in adulthood were at the highest risk of heart disease and type 2 DM (a physiological resistance to insulin action). This finding led to the second part of the hypothesis, the thrifty phenotype (Figure 53.1). The authors proposed that the process of adaptation to undernutrition in fetal life leads to permanent metabolic and endocrine changes. These are beneficial if the undernutrition persists after birth, but may predispose the individual to obesity and impaired glucose tolerance if it does not. The most unfavorable growth pattern is smallness and thinness at birth, continued slow growth in early childhood, followed by an acceleration of growth so that height and weight approach the population means, with a continued rise in body mass index above the mean. The growth pattern differs by sex^{6,23} and ponderal index.⁶ However, as birth weight and ponderal index, as well as body mass index, are only crude measures of the manner in which fetal nutrition affects body composition and the balance of lean body mass to fat, the true impact of fetal growth on later disease remains unclear. Be that as it may, there is no doubt that low birth weight and high body mass index interact and that their effects on BP and impaired glucose tolerance are multiplicative.⁶

The thrifty phenotype paradigm has stimulated a wealth of animal and human research on FGR and its sequelae. The hypothesis predicts that a population undergoing a transition from poor to better nutrition will be characterized by more heart disease and impaired glucose tolerance. This is epitomized by the rapidly rising incidence of type 2 DM, ischemic heart disease, and obesity in increasingly

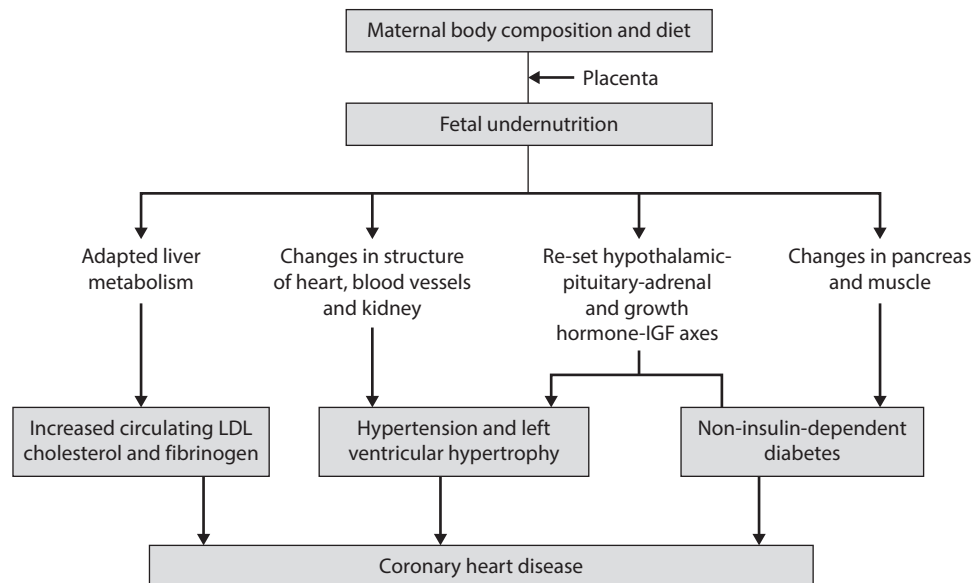


Figure 53.1 Possible mechanisms linking fetal undernutrition and coronary artery disease. IGF, insulin growth factor.

urbanized India.^{24–26} Indian infants are exceptionally small, with a mean birth weight of 2700 g, and their mothers tend to be short and underweight. The infants also have low muscle mass, small viscera, and a relative excess of fat—a body composition particularly likely to lead to insulin resistance.²⁷ In a cohort study in Indian children, Yajnik et al.²⁸ showed that lower weight at birth and higher body mass index in childhood were associated with impaired glucose tolerance. Although improving the growth and nutrition of the mother before pregnancy would seem to be the ideal strategy to improve fetal growth, animal studies have shown that more than one generation of improved maternal nutrition may be necessary for an optimal outcome.^{29,30} Thus, in India, where women begin childbearing already in their teens, before they are fully grown, postponing marriage might be a good first step.³¹ There is only limited evidence that nutritional supplements in pregnancy improve fetal growth in undernourished mothers.³² Furthermore, the effect of supplements varies according to the stage of pregnancy: giving them early in pregnancy may even worsen fetal growth.⁶

Stene et al.,³³ in a large population-based cohort study, noted a relatively weak but significant and nearly linear association between birth weight and risk of type 1 DM. The ratio of children with a birth weight of 4500 g or more to children with a birth weight of less than 2000 g was 2.21. This finding raised the possibility that perinatal factors influence the risk of type 1 DM. The underlying mechanisms of this association are unknown, but they probably differ from those responsible for the association between low birth weight and later onset of type 2 DM.

There may also be factors other than nutrition that play a role in the casual pathway leading to high BP, cardiovascular disease, or type 2 DM.

The fetal origin of adult disease (FOAD) hypothesis assumes that a poor nutrient supply during a critical period of in utero life may “program” a permanent structural or functional change in the fetus, altering the distribution

of cell types, gene expression, or both. Some researchers have accused the authors who formulated the hypothesis of incorrect statistical interpretations because of chance, artifacts, or confounding factors in later life, but these have been resolved.³⁴ Nevertheless, it should be emphasized that support for the hypotheses comes mainly from studies in rodents³⁵ that cannot rule out environmental causes, particularly those associated with socioeconomic status,^{36,37} genetic predisposition to low birth weight or hypertension and hypertension-related diseases, and postnatal factors.^{38,39} Unfortunately, testing these parameters in humans is neither ethical nor practical.

In an attempt to separate genetic from extrauterine environmental influences, some researchers have studied multiple pregnancies. For example, the Tasmanian Infant Health Survey of a cohort of monozygotic, dizygotic, and singleton pregnancies reported a stronger association between birth weight and BP in children from multiple pregnancies.⁴⁰ The association also held true within the monozygotic pairs, suggesting that a genetic predisposition may need to be combined with specific mechanisms within the fetoplacental unit.⁴⁰ A study of 492 pairs of female twins showing an inverse relationship of birth weight and adult BP⁴¹ proved further corroboration for the assumption that restricted intrauterine growth is due to placental dysfunction rather than inadequate maternal nutrition or genetic factors.

Two other studies stress the importance of primary prevention of high BP and cardiovascular disease and the controversy still surrounding Barker’s fetal origin hypothesis. In the first, school children with a history of low birth weight were found to have impaired endothelial function and a trend toward carotid stiffness, which may represent early expressions of vascular compromise.⁴² However, another group of investigators showed no difference in flow-mediated endothelial-dependent vasodilatation (early stage in the development of atherosclerosis) between adolescents who had a low birth weight and controls.⁴³

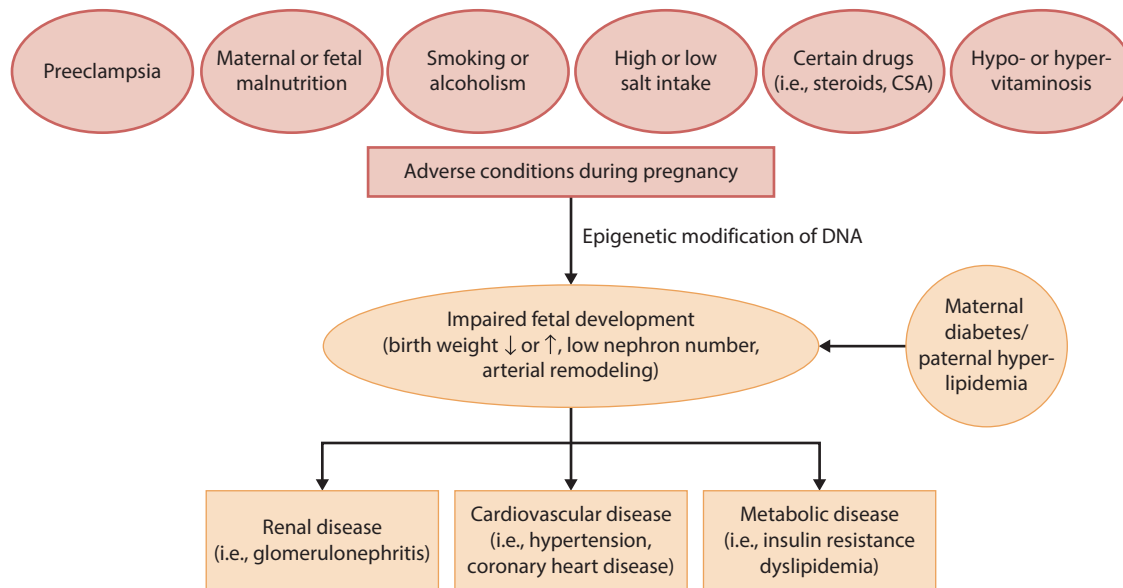


Figure 53.2 Factors that directly or indirectly affect fetal development and may thus favor programming diseases that occur in later life. (From Koleganove, N. et al., *Nephrol. Dial. Transplant.*, 27, 3003, 2012. With permission.)

An additional factor that may underlie the proposed contribution of the intrauterine environment to adult disease is the reduced nephron mass documented in infants in disadvantaged populations with intrauterine growth restriction and exposure to maternal diabetes and vitamin A deficiency. A lower nephron mass may impair nephrogenesis, thereby increasing the susceptibility of the infant to later kidney damage from diseases such as hypertension and diabetes or diabetic kidney, which also commonly affect disadvantaged people.^{44,45}

In summary, the FOAD hypothesis is not without criticism, implying that the association between anthropometric measures at birth and outcomes in adulthood is also influenced by confounders, such as socioeconomic status and lifestyle (diet, cigarette smoking, physical exercise).⁴⁶ Nevertheless, it is likely to remain an important perspective and better position as part of a broader life course perspective rather than as an independent hypothesis.⁴⁷ Recently, the World Health Organization included low birth weight as a risk factor for cardiovascular disease (Figure 53.2).

Vicious cycle of pregnancy: The contributing factors to adult disease

Intrauterine environment component

Successful pregnancy requires normal placental function from adequate placentation early in pregnancy to sustained placental function in the second half of pregnancy. Abnormal placentation, which is defined as defective remodeling of the uteroplacental arteries, results in inadequate uteroplacental blood flow,⁴⁸ leading to unsuccessful pregnancy outcome. In recent years, it has become clear that poor placentation occurs in a broader range of pregnancy complications than initially thought. These complications include preeclampsia

with or without FGR, FGR without hypertension, intrauterine fetal death, placental abruption, and even preterm labor.⁴⁹ Defective deep placentation is dependent upon genetic and environmental factors, as well as time of onset, duration, and extent of the ischemic insult. Moreover, evolutionary pressures derived from the potential conflict relationship between the fetus and the mother that include their response to insults also play a role in determining the phenotypic expression of disorders of the placental bed.⁴⁹ FGR is caused by placental dysfunction, resulting in impaired transfer of oxygen and nutrients to the fetus that may lead to fetal hypoxia and early growth impairment. To assess the vascular function of the placenta in FGR and to estimate the hemodynamic condition of the growth-restricted fetus, Doppler ultrasonography is widely used. Hemodynamic deterioration in cases of severe placental insufficiency is well recognized through the increased impedance to blood flow in the umbilical artery (UA)⁵⁰ and the compensatory mechanisms that maintain cerebral oxygen supply.⁵¹ There is a significant association between pathological Doppler flow pattern and placental vascular compromise. Indeed, the placental component has been studied thoroughly in FGR,^{52,53} with and without pathological UA Doppler indices.^{54,55} Stereological studies observed substantial changes in placental morphology demonstrating poor growth of villi and fetal vasculature of FGR placentas.⁵⁶ Most of the studies included patients with hypertensive disorders.⁵⁷

The fetus, in response to placental undernutrition and in order to maintain sufficient vascular supply to the brain, by using mechanisms such as arterial redistribution, decreases resistance to blood flow in the middle cerebral artery, a phenomenon that has been termed as a “head sparing effect.” Simultaneously, Doppler studies demonstrate that because of the limited blood supply to the fetus, the arterial redistribution process is accompanied by an increased resistance

to flow to other fetal vital organs, such as the kidneys, liver, and pancreas. These independent Doppler studies may shed light on the thrifty phenotype paradigm and on the association between poor intrauterine environment and disease at adulthood. The arterial redistribution as a compensation mechanism may explain why individuals exposed to ischemic changes in utero develop dyslipidemia, lower nephron number, and impaired glucose tolerance, all contributing to metabolic syndrome later in life.

Maternal component: Genetics plus environment

The association between pregnancy complications in general and preeclampsia in particular to future metabolic syndrome is well established in recent years.⁵⁸ By the environmental changes, either metabolic or hormonal, pregnancy complications, especially preeclampsia and GDM, occur in women with underlying vascular compromise.⁵⁹ The same women who develop pregnancy complications are more obese, have more familial history of diabetes and hypertension, and have the same risk factors to develop later atherosclerotic cardiovascular disease. Indeed, our group⁶⁰ and another investigator clearly demonstrated an association between early thrombo-occlusive disorders before the age of 50 and history of pregnancy complications.⁶¹ One of the most common complications in their pregnancy was FGR (odds ratio [OR] of 8.4).⁶⁰ Another investigator demonstrated that preeclamptic women have a 4.3 times increased odds of having a fetus with growth restriction compared to controls.⁶²

Postnatal period component

When undernutrition during early development is followed by improved nutrition later in development, many mammals retain some capacity to compensate by increasing their growth rate. Such compensatory changes will carry costs. This may explain why rapid childhood growth, especially in people who were born small or were thin in infancy, appears to have deleterious effects on later health.^{63,64}

Combined component: The epigenesis

Developmental plasticity is defined as the ability of an organism to develop in various ways, depending on the particular environment or setting.⁶⁵ Developmental plasticity requires stable modulation of gene expression, and this appears to be mediated, at least in part, by epigenetic processes such as DNA methylation and histone modification. Thus, both the genome and the epigenome interactively influence the mature phenotype and determine sensitivity to later environmental factors and the subsequent risk of disease.⁶⁶ The human placenta executes a complex of specific functions influenced by maternal, fetal, and environmental signals. It is highly possible that placental epigenome is linked to its development and function, in general, and between its imprinting status and fetal growth, in particular.⁶⁷

In summary, pregnancy is a key point in the FOAD hypothesis. The maternal background that leads to pregnancy complications and placental compromise is expressed through various mechanisms including genetic and epigenetic mechanisms in the intrauterine and postnatal environment, all contributing factors to adult disease (Figure 53.3).

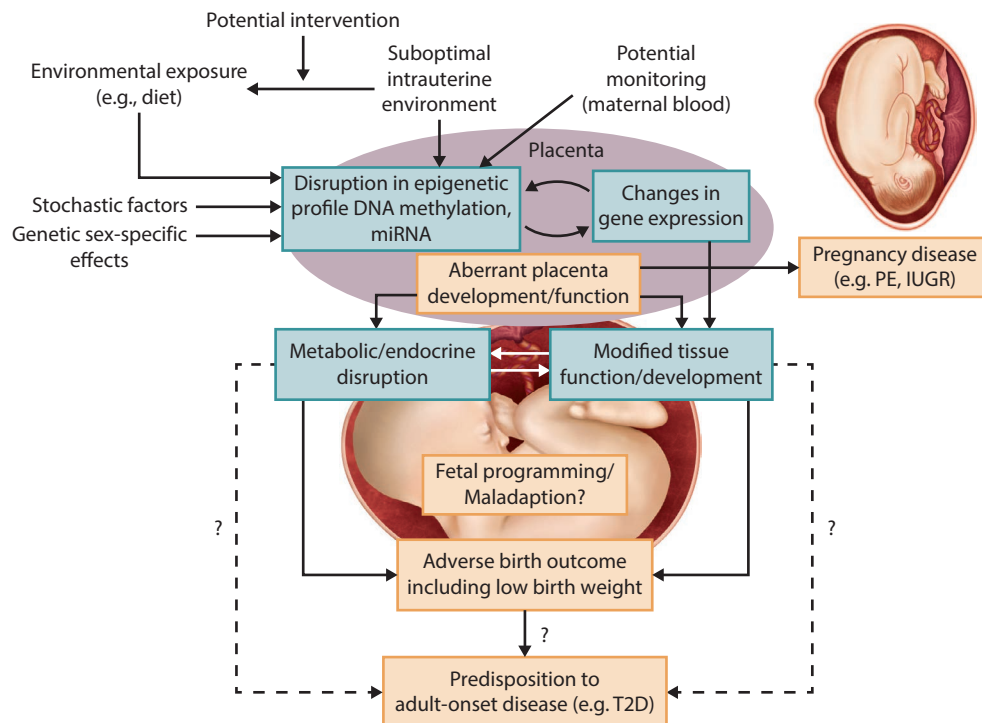


Figure 53.3 Influences and consequences of placental epigenetic disruption. Several factors are known to influence placental epigenetic profile, including environmental exposures, stochastic events, and genetic and sex effects. Disruption of DNA methylation patterns can lead to aberrant gene expression and placental development and function. In turn, placental dysfunction can lead to pregnancy-associated disease as preeclampsia or fetal growth restriction. Disruptions in normal fetal development can lead to predisposition to adult-onset disease and health problems. (From Novakovic, B. and Saffery, R., *Placenta*, 33, 959, 2012. With permission.)

Mechanisms underlying metabolic syndrome

Metabolic syndrome is characterized by a cluster of clinically recognizable physiological abnormalities: glucose intolerance, high BP, and unfavorable lipid profile—all alterations induced by the compensatory hyperinsulinemia. It also involves biochemical abnormalities.⁶⁸ Upregulation of the inflammatory cascade has been recognized as an additional risk factor for the impaired cardiovascular component of the syndrome.⁶⁹

Insulin resistance now appears to be the epidemiological link between high BP and obesity. Insulin resistance induces hypertension via mechanisms at the cellular, circulatory, and neurological levels as well as via possible polygenic factors. Acquired or transient insulin resistance is associated with certain physical conditions, such as pregnancy, obesity, oral contraceptive use, and severe distress. Type 2 DM is a state of increased insulin secretion caused by the physiological resistance of insulin action and a lower-than-normal beta-cell reserve. Diabetes in pregnancy or gestational DM (GDM) may precede the clinical expression of type 2 DM in the nonpregnant state, even by several years. Preeclampsia and other hypertensive disorders, which are known to have a higher incidence in GDM, can be linked to increased insulin resistance.⁷⁰

Insulin resistance and hypertension in the nonpregnant state

To understand the association between insulin resistance and hypertensive disorders in pregnancy, we first need to elucidate the role of insulin resistance in hypertensive disorders in the nonpregnant state. The pathogenesis of essential hypertension is multifactorial, involving complex interactions between endocrine, metabolic, and genetic factors.

Obesity component

The worldwide obesity epidemic has been a major driving force in the recognition of metabolic syndrome.⁶⁸ Several of the definitions proposed for metabolic syndrome include increased waist circumference.^{70,71} This factor is known to be associated with a relative predominance of visceral over subcutaneous adipose tissue,^{72,73} which results in a higher rate of flux of adipose-tissue-derived free fatty acids to the liver through the splanchnic circulation, thereby effecting glucose production, lipid synthesis, and prothrombotic protein secretion—all features of metabolic syndrome.⁷³ Obesity, aging, and diabetes can amplify genetic tendencies toward the clinical expression of the disorder (Figure 53.4). Familial clustering of DM and hypertension has been reported by several investigators, who also observed a close association of insulin resistance with obesity-related hypertension.^{74,75}

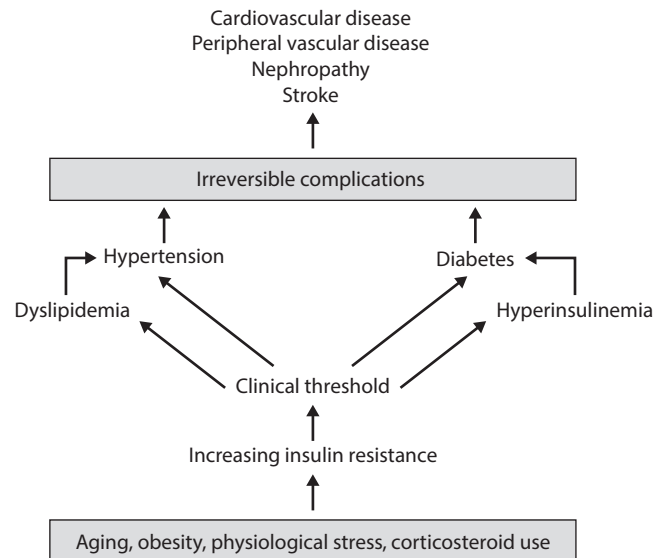


Figure 53.4 Factors influencing the generation of insulin resistance and its clinical correlates in the nonpregnant state.

Dyslipidemia component

Several other metabolic disturbances, such as elevated levels of triglycerides, decreased levels of high-density lipoproteins, high cholesterol level, glucose intolerance, and hyperuricemia, have also been related to hyperinsulinemia.⁷⁶ The metabolic consequences of these disturbances include changes in the lipid profile, resulting in atherosclerosis, increased deposition of body fat, and proliferation of vascular smooth muscle cells, which place the hypertensive, hyperinsulinemic individual at increased risk of cardiac complications and stroke.⁷⁷ Studies of the evolution of the clinical and biological disturbances in women with a polycystic ovary (PCO) support the view that insulin resistance, dyslipidemia, and hypertension are all manifestations of a single syndrome. Often obese, these women have hyperinsulinemia that disrupts sex hormone production,⁷⁸ resulting in androgenization and clinical manifestations of hirsutism and infertility. During pregnancy, they have more glucose intolerance⁷⁹ and pregnancy-induced hypertension (PIH).⁸⁰ Later in life, women with PCO acquire a male-pattern risk profile for coronary artery disease, including dyslipidemia and hypertension.⁸¹

Inflammatory component

The association of the metabolic syndrome with inflammation is well documented.⁸² The increase in proinflammatory cytokines, including interleukin-6, resistin, tumor necrosis factor alpha (TNF- α), and C-reactive protein,⁸³ reflects an overproduction by monocyte-derived macrophages and possibly other cells within the expanded adipose tissue mass.^{84–86}

Mechanisms of action

Physiological studies suggest that insulin resistance occurs primarily in the peripheral muscles and is mediated through the nonoxidative intracellular pathways of glucose disposal.

Insulin modulates BP through several pathways, including stimulation of sympathetic neural activity, direct vasculopathic actions, changes in cellular ion flux, and promotion of sodium retention.^{87–89}

Clinical consequences of insulin resistance

Insulin resistance impairs glucose tolerance while promoting dyslipidemia, obesity, hypertension, and atherosclerosis. Patients with three or more of these risk factors have an increased incidence of stroke, nephropathy, ischemic heart disease, and peripheral vascular disease.⁹⁰ Long-term diabetic complications are the most common cause of blindness, renal failure, and limb amputation in the United States today. Meticulous glycemic control has been shown to decrease the incidence of eye disease among diabetic patients. Antihypertensive therapy, specifically with angiotensin-converting enzyme inhibitors (ACE-Is), is effective in reducing the rate of progression of diabetic kidney disease. To prevent the peripheral vascular remodeling that results in stroke, limb loss, and heart disease, the underlying pathophysiological mechanism needs to be reversed. This has become possible with the introduction of metformin⁹¹ and troglitazone,⁹² which are prototypes of the new classes of insulin-sensitivity-enhancing agents. These drugs are an important addition to the weight loss, exercise, and diet modification programs used to date, lifestyle habits that are effective but rarely adhered to for more than a few years.

Insulin resistance and type 1 DM

The recent acceptance of the role of insulin resistance in type 1 DM was supported by the concurrent rise in the incidence of the disease with a steady increase over the last 20–30 years in overweight and sedentary habits in children and adolescents in many populations. Medical evidence of the link between type 1 DM and insulin resistance/metabolic syndrome continues to grow. The insulin resistance associated with the rising prevalence of weight gain may reflect a more aggressive form of autoimmune disease mediated by the same immuno-inflammatory factors that mediate beta-cell destruction, namely, TNF- α and interleukin-6.⁹³ Moreover, the onset of diabetic nephropathy might contribute to insulin resistance/metabolic syndrome via mechanisms of low-grade inflammation and increased oxidative stress.^{94,95} These concepts are included in the “accelerator hypothesis” on the role of insulin resistance and overweight in type 1 DM.⁹⁶

Insulin resistance and hypertension in pregnancy

In normal pregnancy, insulin resistance results in a metabolic advantage for the fetus. The mother enters a state of accelerated starvation in which she increases her reliance on lipolysis and protein catabolism as a source of energy. Thus, glucose is reserved for the fetus, which uses it as its

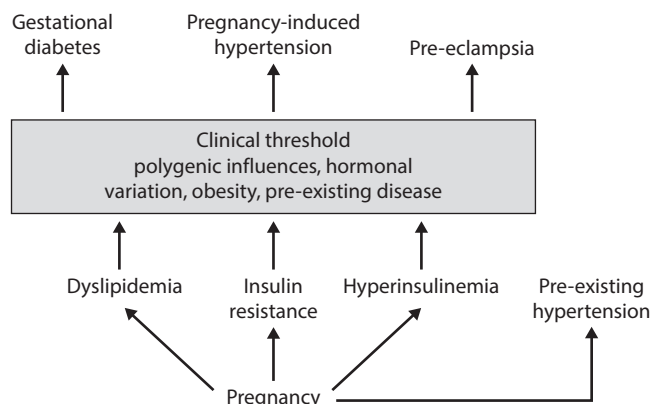


Figure 53.5 Risk factors for vascular disease and metabolic syndrome in pregnancy.

primary fuel.⁹⁷ A steady supply of glucose is essential for the growing fetomaternal unit; normally, pregnant women are able to increase their insulin secretion to three times that of nonpregnant women.⁹⁸ In GDM, however, there is no increase in maternal insulin secretion in reaction to the increasing insulin resistance.⁹⁹ Some investigators believe this effect is due to a metabolically limited beta-cell reserve.^{100,101} In most women with GDM, insulin sensitivity is restored after pregnancy. However, some may later develop type 2 DM. The reported cumulative incidence rate of type 2 DM after GDM is approximately 50% after 5 years.^{102,103} It is even higher in women with excessive weight gain or with repeated pregnancies, who continue to experience insulin resistance.¹⁰⁴ Thus, the strong association between insulin resistance, hypertension, obesity, and dyslipidemia, as part of the metabolic syndrome or sharing a common pathway in intrauterine life, may explain the higher incidence of hypertensive complications in diabetic pregnancy. Researchers reported that metabolic syndrome may also involve other metabolic abnormalities besides hyperglycemia, hyperinsulinemia, and dyslipidemia, namely, increased concentrations of plasminogen activator inhibitor-1,¹⁰⁵ leptin,¹⁰⁶ and TNF- α .¹⁰⁷ Although these markers are surrogate measures of insulin sensitivity, they have been associated with a risk of hypertension in pregnancy. In fact, the normal physiological response to pregnancy has several components, such as insulin resistance, hyperlipidemia, increase in coagulation factors, and upregulation of the inflammatory cascade, which may contribute to a transient and earlier than expected excursion into metabolic syndrome¹⁰⁸ (Figure 53.5).

Gestational diabetes and hypertensive disorders

The study of both GDM and PIH has suffered from the lack of international consensus about classification, definitions, and nomenclature, leading to difficulties in comparing studies that used different diagnostic criteria. Nevertheless, epidemiological and physiological evidence suggests that GDM and PIH are etiologically distinct entities and that GDM is strongly associated with insulin resistance and glucose intolerance, whereas preeclampsia is probably not.

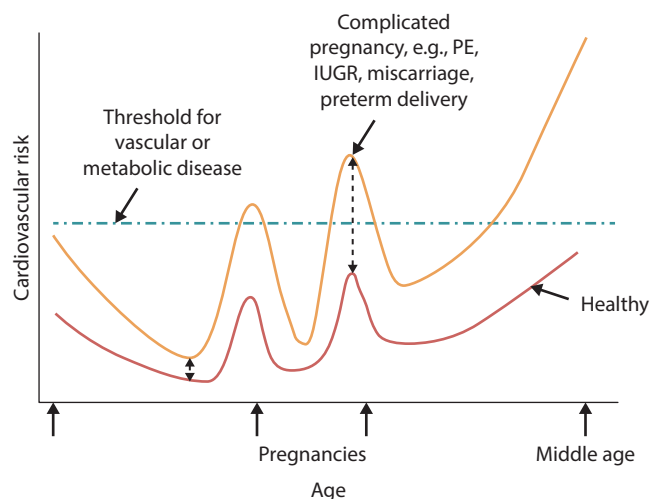


Figure 53.6 Factors influencing the generation of insulin resistance and its clinical correlates during pregnancy. (From Sattar, N. and Greer, I.A., *Br. Med. J.*, 325, 157, 2002. With permission.)

Epidemiological studies

Diabetic pregnancy is associated with a higher rate of hypertensive complications than normal pregnancy^{109,110} and a slightly increased risk of preeclampsia (15%–20% vs 5%–7%).^{111–113} The latter holds true even when the diagnosis of GDM is based on the 2 hour 75 g oral glucose tolerance test.¹¹⁴ Mean arterial pressure is further increased in the presence of early diagnosis of GDM and the need for insulin therapy.¹¹⁵

The increased risk of hypertensive disorders in GDM is probably a result of the combination of insulin resistance and a genetic predisposition (Figure 53.6). A genetic predisposition to PIH was described in southwestern Navajo Indians, who like other Native Americans are also at increased risk of hypertension, obesity, and DM.¹¹⁶ Preeclampsia was also reported to be associated with increased fasting plasma insulin levels in African-American women.¹¹⁷ However, these findings have not been confirmed in more heterogeneous populations.¹¹⁸

Physiological studies

Patients with the severest form of glucose intolerance are more likely to exhibit preeclampsia¹¹⁹ than patients with milder forms.¹¹⁸ Controlled studies of the association between insulin resistance and preeclampsia have been performed in several populations. Martinez et al.¹²⁰ found that among women with normal glucose tolerance in the third trimester, those who subsequently developed severe preeclampsia had similar fasting and postprandial glucose levels to normotensive controls, but their fasting plasma insulin levels were twofold higher and their postload insulin concentrations fourfold higher. Moreover, Joffe et al.¹²¹ reported that the level of plasma glucose at 1 hour after a 50 g oral glucose challenge was an important predictor of preeclampsia, even if it was within the normal range. This suggests that there is a continuum of insulin resistance also in women with normal glucose tolerance that may predispose them to hypertensive disease. This assumption was supported by a

similar study in China wherein higher serum insulin concentrations were detected in women with preeclampsia.¹²² Besides insulin resistance, women with GDM and women with preeclampsia have similar hemodynamic profiles, namely, significant left ventricular hypertrophy and reduced diastolic function.¹²³ The mechanism by which insulin resistance may link these physiological findings is still unknown. One possibility is an interference of insulin resistance with the function of an endogenous sodium pump inhibitor or digitalis-like factor. Graves et al.¹²⁴ demonstrated that levels of serum digoxin-like immunoreactive factor are higher in women with preexisting diabetes and preeclampsia than in normotensive diabetic women.

In hypertensive diabetic patients, some of the physiological changes that occur during pregnancy may persist after pregnancy. In one study, women with a preeclamptic pregnancy showed greater plasma insulin responses and steady-state plasma glucose levels 2 months after delivery than women with uncomplicated pregnancy.¹²⁵ A longer-term study reported persistent mild hyperinsulinemia in women 17 years after a preeclamptic pregnancy, despite their current normoglycemic state.¹²⁶ Other investigators, however, failed to detect these changes at 3–6 months after delivery.¹²⁷

Pregestational diabetes and hypertensive complications

In most cases, pregestational diabetes refers to type 1 DM. The incidence of type 1 DM in pregnancy ranges from 0.2% to 0.5%.^{128,129} Affected women contribute heterogeneous group in terms of duration of diabetes, White's classification, the presence of hypertension, and end-organ damage, especially to the eye (retinopathy) and kidney (nephropathy). Pregnancy in women with type 1 DM is associated with increased risks of preeclampsia, intrauterine growth restriction (IUGR), neonatal morbidity, and perinatal mortality.^{129–135} The diagnosis of preeclampsia is difficult in women with preexisting hypertension and proteinuria,^{129,136} and women with chronic hypertension are at increased risk of superimposed preeclampsia independent of the presence of diabetes.¹³⁷ The rate of hypertensive disorders (PIH and preeclampsia) in the various studies ranged from 9% to 66%. The lowest rate occurred in women with milder forms of DM (class B) and the highest in women with diabetic nephropathy. Table 53.1 summarizes the reported rates of preeclampsia in women with type 1 DM.^{128,130,138–141} Four of the six studies noted that rates of preeclampsia increased with an increasing severity of diabetes, with a mean of 16% (range 9%–24%). Rates were higher in patients with diabetic nephropathy (mean 52%, range 35%–66%) (Table 53.2). The risk factors identified for preeclampsia in women with type 1 DM were as follows: duration of diabetes, preexisting hypertension, microalbuminuria prior to pregnancy, glycemic control prior to 20 weeks, nulliparity, minimal proteinuria (190–499 mg/dL) before 20 weeks, and nephropathy.^{118,131,132,142–144} Siddiqi et al.¹³¹ listed nulliparity, duration of diabetes, and poor glycemic control, and Caritis et al.¹⁴² nulliparity and mean arterial pressure. Combs et al.¹³² added glycohemoglobin (HbA1c) level >9% at 12–16 weeks of

Table 53.1 Rate of preeclampsia in women with type 1 diabetes (excluding those with nephropathy)

Authors	No. of women	White's class	Preeclampsia ^a	
			No.	%
Hanson and Persson ¹²⁸	463	B–R	53	11.5
Garner ¹²⁹	107	B,C	13	12.2
Greene et al. ¹³⁰	361	B–R	86	23.8 ^a
Miodovnik et al. ¹³⁸	136	B–R	12	9
Kovilam et al. ¹³⁹	238	B–D	36	15
Sibai et al. ¹⁴⁰	462	BD	92	20
Total	1767		292	16.4

^a Includes women with pregnancy-induced hypertension.

Table 53.2 Rate of preeclampsia in women with diabetic nephropathy

Authors	No. of women	Preeclampsia ^a	
		No.	%
Hanson and Persson ¹²⁸	31	18	58
Greene et al. ¹³⁰	59	39	66
Gordon et al. ¹³³	45	24	53
Reece et al. ¹³⁵	31	11	35
Miodovnik et al. ¹³⁸	46	30	65
Kovilam et al. ¹³⁹	73 ^a	32	44
Sibai et al. ¹⁴⁰	58	21	36
Bar et al. ¹⁴⁴	24	11	46
Total	367	186	52

^a Includes women with retinopathy and nephropathy.

gestation and proteinuria >190 mg/dL. Accordingly, Hanson and Persson¹²⁸ noted a preeclampsia rate of 31% when HbA1c levels were >10.1% and a rate of 10.2% when HbA1c levels were <10.1%. These findings indicate that PIH/preeclampsia might be preventable by aggressive control of maternal BP before and during pregnancy and prevention of microalbuminuria or reduction of proteinuria level in women with diabetic nephropathy. Recently, researchers found that suboptimal control of hypertension in early pregnancy was associated with a significant risk of preterm delivery.¹⁴⁵

ACE-Is seem to be the ideal agent for the treatment of hypertension.^{144,146} According to one long-term follow-up study, the survival of patients with diabetic nephropathy has increased from 5 to 7 years to a median of 21.7 years, most likely because of improvements in aggressive antihypertensive treatment and glycemic control.¹⁴⁵ The same group of investigators showed that pregnancy itself has no adverse impact on kidney function and survival in patients with preserved renal function and diabetic nephropathy.¹⁴⁷ Therefore, in women with type 1 DM and preexisting hypertension and proteinuria, stringent glycemic control should be started at least 6 months before conception in order to achieve a good

pregnancy outcome and long-term effect.¹⁴⁴ However, contrary to findings in earlier studies of a nonteratogenic effect of ACE-I in early pregnancy,^{148,149} in 2006, Cooper et al.¹⁵⁰ reported an increased risk of major congenital malformations in infants who were exposed to ACE-I in the first trimester compared to infants who were not (OR = 2.71, 95% CI 1.72–4.27). Other investigators found no increased risk of major congenital malformations.¹⁵¹ Nevertheless, ACE-Is are still useful for patients with diabetic nephropathy for a planned pregnancy. Since conception can take months, preventing the administration of ACE-I during this period may enhance long-term renal function and pregnancy outcome. Patients should be advised to use sensitive pregnancy kits for the earliest possible detection of pregnancy, when the ACE-I must be immediately stopped. The preconception medication should be accompanied by strict glycemic control better achieved by the use of insulin pumps, rather than multi-injections.¹⁴⁴ Some authors suggested the use of low-dose aspirin to prevent preeclampsia, since alterations in the metabolism of prostacyclin and thromboxane A2 have been reported in DM.^{129,152} However, Caritis et al.,¹⁵² in a study of 462 women with type 1 DM, found no significant differences

in the rate of preeclampsia between the aspirin and placebo groups, although there was a nonsignificant trend toward a lower rate of preeclampsia in the aspirin group (19% vs 32%, respectively). Larger studies in patients with diabetic nephropathy are needed to clarify this issue. The steady increase in overweight in developed countries, concurrent with the rising incidence of type 1 DM discovered a new entity of women with pregestational DM with overweight and obesity. In the subgroup with diabetic nephropathy, maternal overweight was recently found to be associated with increased risk of pregnancy complications.¹⁵³ Therefore, these women should be advised to reduce weight, in addition to the prepregnancy counseling program.

Microalbuminuria, diabetes, and hypertension in pregnancy

The role of microalbuminuria in DM has been established over the last 20 years. At the early stage of DM, when glucose metabolism is not controlled, the increase in glomerular plasma flow and intraglomerular pressure is probably responsible for the increased protein excretion.¹⁵⁴ Some authors believe these hemodynamic alterations are major determinants of both the initiation and progression of diabetic nephropathy.¹⁵⁵ Several studies have reported that patients with type 1¹⁵⁶ or type 2 DM¹⁵⁷ who have above-normal urinary albumin excretion rates are more likely to acquire diabetic nephropathy, eventually progressing to renal failure.¹⁵⁶ Microalbuminuria is also associated with

an excess of known and potential cardiovascular risk factors, and it is a marker of established cardiovascular disease in both hypertensive¹⁵⁸ and nonhypertensive¹⁵⁹ individuals. Its role in diabetic and hypertensive pregnancy is less clear,¹⁶⁰ but becoming increasingly recognized. One study found that the presence of microalbuminuria in the early third trimester was predictive of preeclampsia in pregnant women at risk.¹⁶¹ Furthermore, a significantly higher rate of women whose pregnancy was complicated by preeclampsia had microalbuminuria 5 years later (40%) than women with uncomplicated pregnancy.¹⁶² Microalbuminuria was also noted in 30% of 72 women who had not conceived since GDM pregnancy 5–8 years previously—a significantly higher rate than in women who did not have a history of GDM.¹⁶³ Ekblom,¹⁴³ in a study of 68 women with type 1 DM, found that preeclampsia developed in 60% of those who had microalbuminuria before pregnancy. When the data were fitted to a logistic regression model, a significant association was revealed between microalbuminuria and duration of diabetes and preeclampsia. Similar in patients with hypertension, the progression to diabetic nephropathy in patients with type 1 DM and microalbuminuria can be slowed by blockade of the renin–angiotensin system. Angiotensin II receptor antagonists were also recently shown to be renoprotective in patients with type 2 DM and microalbuminuria.¹⁵⁸ This finding and other preliminary results^{144,146} further suggest that pregnancy outcome may be improved with prepregnancy ACE-I treatment (discontinued at conception) in diabetic patients with overt proteinuria or microalbuminuria.

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54 Diabetic retinopathy

Nir Melamed and Moshe Hod

Diabetic retinopathy is the most common chronic complication of diabetes mellitus¹ and is the most common cause of blindness in middle-aged subjects in the United States and the United Kingdom.^{2–5} The mutual effects of pregnancy and retinopathy, though long a subject of research and debate, remain unclear, and data on methods of diagnosis and management in pregnancy remain scarce.^{6–10} The purpose of this chapter is to review the current literature on the effects of pregnancy on diabetic retinopathy and to provide guidelines for the management of pregnancies complicated by diabetic retinopathy.

Diabetic retinopathy in nonpregnant patients

Epidemiology

The prevalence of diabetic retinopathy is almost 100% in patients with type 1 diabetes and over 60% in patients with type 2 diabetes in whom the disease has been present for more than 20 years.^{11–13} In the population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy, the prevalence of proliferative diabetic retinopathy was 1.2% and 67% in persons with type 1 diabetes for less than 10 years and more than 35 years, respectively.

It is estimated that 20%–30% of diabetic women in the reproductive age group have some evidence of retinopathy.¹ Risk factors for diabetic retinopathy include longer duration of the disease, onset of disease before 30 years of age, poor glycemic control manifested by higher levels of glycosylated hemoglobin, hypertension, hypertriglyceridemia, anemia, and evidence of diabetic nephropathy.^{4,11,14–21}

Classification of diabetic retinopathy

Diabetic retinopathy is a progressive disorder and is generally categorized as either nonproliferative (NPDR, or background) or proliferative, although more detailed grading systems exist,^{22,23} as presented in Table 54.1. Grading is performed according to the semiquantitative assessment of the morphological lesions on fundus photographs. The grading system considers mainly the type and number of retinopathy lesions, while the diagnostic value of the regional distribution of the lesions is largely unknown.²⁴

Pathogenesis and natural history

Diabetic retinopathy is the result of several pathological processes that include loss of capillary pericytes, damage to capillary wall resulting in increased permeability and weakness of capillary wall, microvascular occlusion leading to retinal ischemia, and proliferation of new blood vessels.^{25–28} It is currently believed that chronic hyperglycemia is the primary cause of diabetic retinopathy.^{29–31} Although the exact mechanisms by which hyperglycemia initiates these pathological processes remain unclear, putative mechanisms include impaired autoregulation of retinal blood flow (RBF),³² increased production of sorbitol by the enzyme aldose reductase,³³ accumulation of advanced glycation end products,³⁴ oxidative stress,^{35–37} increased platelet aggregation and hypercoagulability,³⁸ and alteration in cell signaling pathways such as diacylglycerol-induced protein kinase C activity.^{39–41}

Nonproliferative diabetic retinopathy

Microaneurysms, hypercellular outpouchings from the capillary wall, are the earliest signs of diabetic retinopathy. They appear as small red dots (Figure 54.1) and can be identified in 2% and 98% of the patients with type 1 diabetes in whom the disease has been present for 2 and 15 years, respectively.⁴² Possible mechanisms for the formation of microaneurysms include weakness of capillary wall and increased intraluminal pressure.^{25,26} Rupture of microaneurysms results in retinal hemorrhages that may appear as either small dots or larger flame-shaped hemorrhages. As a result of the increased capillary permeability, lipids and proteins leak into the outer retina, appearing as well-defined yellow-white deposits, known as hard exudates (Figure 54.2). Extravasation of fluids may lead to retinal thickening and edema. Although, in general, nonproliferative retinopathy does not impair vision, hard exudates or retinal edema involving the macular area may lead to severe loss of central vision.⁴³ Thus, diabetic macular edema (DME) is the most common cause of vision loss in NPDR.⁴⁴

Preproliferative diabetic retinopathy

As the disease progresses, retinal capillaries become occluded, leading to retinal ischemia. This stage, known as preproliferative retinopathy, is characterized by the

Table 54.1 Diabetic retinopathy severity scale

Classification	Description
Normal	No evidence of retinopathy
Nonproliferative	
Minimal	Microaneurysms only
Mild	Microaneurysms plus hard exudates, soft exudates (cotton wool spots), mild retinal hemorrhages, venous loops
Moderate	Microaneurysms plus mild intraretinal microvascular abnormalities (IRMA), moderate retinal hemorrhages, venous beading
Severe	Microaneurysms plus moderate to severe IRMA, severe retinal hemorrhages, venous beading
Proliferative	
Proliferative	New vessels in the retina or on the optic disc
High-risk proliferative	Proliferative plus preretinal hemorrhage, fibrous tissue, or other high-risk characteristics
Advanced diabetic eye dis.	Proliferative plus vitreous hemorrhage, retinal detachment, or rubeosis iridis

Source: Adapted from Early Treatment Diabetic Retinopathy Study Research Group, *Ophthalmology*, 98, 786, 1991.



Figure 54.1 Normal fundus.

appearance of white-grayish cotton wool spots (soft exudates), reflecting the accumulation of axoplasmic debris due to ischemia-induced interruption of axoplasmic transport, and by the presence of microvascular abnormalities such as venous beading and loops.²²

Proliferative diabetic retinopathy

The hallmark of proliferative retinopathy is retinal and preretinal neovascularization that occurs in response to the increased retinal ischemia (Figure 54.3).⁴⁵ Presumably, the nutrient-starved retina sends out a chemical message to stimulate the growth of new blood vessels (neovascularization). These vessels often grow on the surface of the retina, at the optic nerve, or on the iris, and are characterized by increased fragility. They may penetrate the outlining

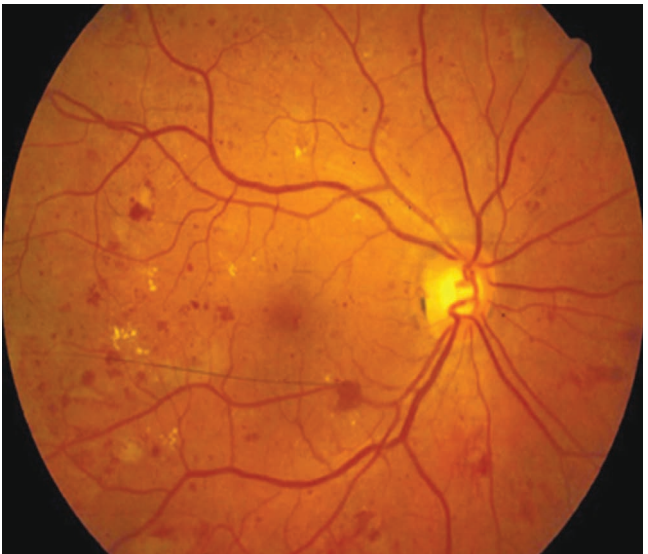


Figure 54.2 Nonproliferative diabetic retinopathy.

membrane of the retina and become adherent, with their accompanying fibrovascular tissue, to the posterior vitreous. Visual loss in patients with proliferative retinopathy may be caused by either vitreous hemorrhage (VH), tractional retinal detachment following vitreous contraction, or neovascular glaucoma.^{44,46,47} Several growth factors have been shown to be involved in the process of neovascularization, including vascular endothelial growth factor (VEGF),^{48–57} insulin-like growth factor 1 (IGF-1),^{58–65} growth hormone (GH),^{66–72} pigment-epithelium-derived factor (PEDF),^{73–79} placental growth factor,⁸⁰ basic fibroblast growth factor,⁸¹ hepatocyte growth factor,^{82–84} and, recently, also erythropoietin.^{85–87}

The Diabetic Retinopathy Study Research Group⁸⁸ has identified four risk factors for severe visual loss in diabetic retinopathy, as shown in Table 54.2. Untreated, affected patients have a 30% and 50% risk of visual acuity deterioration to less than 5/200 within 3 and 5 years, respectively.

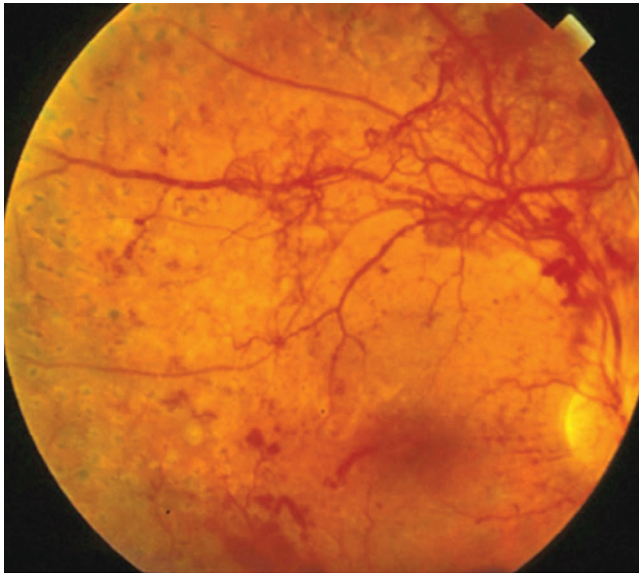


Figure 54.3 Proliferative retinopathy.

Table 54.2 High-risk characteristics for severe visual loss from proliferative retinopathy

1. New vessels on or within one disc diameter of the optic disc and at least one-fourth of the disc area in extent, with or without preretinal or vitreous hemorrhage
2. Any new vessels on or within one disc diameter of the optic disc, with preretinal or vitreous hemorrhage
3. New vessels anywhere in the retina more than one disc diameter from the optic disc and at least one-half of the disc area in extent (including the total area of all new vessels in the ocular fundus), with preretinal or vitreous hemorrhage
4. Extensive preretinal or vitreous hemorrhage that hides probable new vessels meeting the aforementioned criteria

Source: The Diabetic Retinopathy Study Research Group. *Arch Ophthalmol* 1979.

Treatment of diabetic retinopathy

Several preventative and therapeutic interventions have been shown to be effective in reducing the morbidity associated with diabetic retinopathy. Nevertheless, because of the limitations of these interventions, efforts are being made to improve the understanding of the mechanisms responsible for diabetic retinopathy. This may lead to the development of new therapies, several of which are currently under clinical trials.

Glycemic control

Preventing diabetic retinopathy from developing is the most effective approach to preserve vision. The results of the Diabetes Control and Complications Trial (DCCT)^{30,89} have provided clear evidence that intensive glycemic control is associated with a remarkable reduction in the development and progression of diabetic retinopathy in patients with

type 1 diabetes. Subsequent studies supported this finding⁹⁰ and demonstrated similar beneficial effects in patients with type 2 diabetes.^{91–93}

Unexpectedly, it was found that some of the patients with preexisting retinopathy had a transient worsening of their retinopathy after the institution of intensive glycemic control.^{30,94–97} This deterioration manifested as an increase in soft exudates and blot hemorrhages, but progression to proliferative retinopathy was uncommon. Although the reason for this transient worsening is not clear, possible mechanisms include reduced plasma volume or increased levels of growth factors such as IGF-1 and VEGF.^{98–100} Among patients with mild to moderate nonproliferative retinopathy, the long-term benefits of intensive glycemic control exceed the risk of this transient worsening. However, in patients with severe nonproliferative or proliferative retinopathy, photocoagulation may be indicated before intensive glycemic control is initiated.⁹⁴

Multifactorial risk reduction

Control of hypertension, a risk factor for diabetic retinopathy, appears to delay the progression of retinopathy in patients with type 2 diabetes.^{16,21,101} High serum lipid levels are associated with increased risk of hard exudates, macular edema, and proliferative retinopathy.^{102,103} Normalization of lipid levels may reduce this risk.

Antiplatelet agents

The increased platelet aggregation observed in diabetic patients and the evidence of microthromboses in retinal capillaries³⁸ suggested that treatment with antiplatelet agents may be beneficial in diabetic retinopathy. However, in the Early Treatment of Diabetic Retinopathy Study (ETDRS), treatment with daily aspirin had no effect on the development or progression of diabetic retinopathy.^{104,105}

Laser photocoagulation

Argon-laser photocoagulation, which was introduced in the 1950s, is the primary treatment for advanced retinopathy. In the Diabetic Retinopathy Study, panretinal photocoagulation in patients with proliferative retinopathy was associated with 50% reduction in severe vision loss.^{88,106,107} In the ETDRS, the use of panretinal photocoagulation at earlier stages of retinopathy (mild to moderate nonproliferative retinopathy) was not found to be beneficial and was associated with significant loss of visual acuity and peripheral vision.¹⁰⁸ However, focal photocoagulation in areas of vascular abnormality was found to be effective in reducing the risk of moderate visual loss in cases of macular edema.¹⁰⁸ Although the mechanism responsible for the beneficial effect of panretinal photocoagulation is unclear, it was suggested that the destruction of hypoxic regions in the peripheral retina reduces the stimulus for neovascularization.²⁹ Because of the possible side effects associated with panretinal photocoagulation (loss of peripheral vision and impaired night vision), this treatment is usually recommended only in cases of high-risk proliferative retinopathy.¹⁰⁸ However, patients with type 2 diabetes can benefit from laser photocoagulation

at earlier stages of the disease (severe nonproliferative or early proliferative retinopathy).^{108,109}

Vitrectomy

Vitrectomy, which includes removal of the vitreous gel and may be accompanied by removal of fibrous tissue and repair of retinal detachment, is associated with dramatic improvement of vision in cases of severe VH,^{110–112} as well as in cases of very severe neovascularization with no evidence of VH.^{113–117} Vitrectomy may also be achieved by means of pharmacological interventions using enzymes such as hyaluronidase, plasmin, and chondroitinase that have been shown to be effective in clearing VH, thereby avoiding the need for surgery. Plasmin has been used to cleave the vitreoretinal junction and allow less traumatic removal of the posterior hyaloids.^{118,119} These interventions are still under investigation.

Experimental therapies

Better understanding of the mechanisms and factors involved in the pathogenesis of diabetic retinopathy (as described earlier) has led to exploration of new drugs directed against these factors, some of which are currently under clinical trials. Examples include aldose reductase inhibitors,^{33,120–122} protein kinase C inhibitors,¹²³ antioxidants, inhibition of nonenzymatic glycation of proteins (aminoguanidine),¹²⁴ VEGF inhibitors,^{125,126} intraocular gene therapy with the PEDF gene,^{127,128} and somatostatin analogues (reduce GH and IGF-1 levels).¹²⁹

There is some evidence that intravitreal injection of glucocorticoids such as triamcinolone acetonide may be effective in decreasing neovascularization. However, glucocorticoids may be associated with significant risks including increased intraocular pressure, cataract formation, and endophthalmitis.^{130,131}

Inhibition of VEGF has been shown to prevent neovascularization in animal models.^{125,132,133} Several humanized antibodies directed against VEGF have demonstrated promising results in the treatment of proliferative retinopathy. Examples include bevacizumab and ranibizumab that are nonselective anti-VEGF antibodies that are currently being used in the treatment of age-related macular degeneration. Pegaptanib is an oligonucleotide ligand that specifically inhibits VEGF-165, the VEGF isoform that is most important in promoting neovascularization and vascular permeability.^{134,135} There are now several clinical studies demonstrating regression of neovascularization after intravitreal injection of VEGF inhibitors.^{136–144} However, there are only limited data regarding the long-term efficacy and safety of these agents, and more randomized trials are required.

Diabetic retinopathy in pregnancy

Impact of pregnancy on the development and progression of diabetic retinopathy

Understanding the effect of pregnancy on diabetic retinopathy is essential for determining the optimal management of pregnancies complicated by diabetic retinopathy. However,

whether pregnancy influences the development or progression of diabetic retinopathy is still unanswered.¹⁴⁵ Although most studies have reported that pregnancy is associated with progression of retinopathy in 17%–70% of the cases,^{146–158} several studies have failed to support these findings.^{159–163}

Studies supporting a deteriorating effect of pregnancy on diabetic retinopathy

Moloney et al.¹⁴⁸ prospectively followed 53 pregnant women with type 1 diabetes every 6 weeks during pregnancy and until 6 months postpartum. Of the 20 women who had no evidence of retinopathy, 8 (40%) developed retinopathy during pregnancy. Progression of preexisting retinopathy during pregnancy was common, with a moderate increase in the number of microaneurysms and the appearance of retinal hemorrhages and soft exudates in 56% and 28% of the cases, respectively. The risk for the development and progression of retinopathy was related to the duration of diabetes.

Dibble et al.¹⁴⁷ followed 55 pregnant diabetics who were managed by strict glycemic control. Progression of retinopathy was related to the duration of diabetes and the severity of retinopathy before pregnancy. Thus, progression of retinopathy occurred in 16% (3 of 19) of the women with minimal or mild nonproliferative retinopathy compared with 86% (6 of 7) of the women with untreated preexisting proliferative retinopathy. Similarly, in a prospective cohort study of 145 pregnant women with type 1 diabetes,¹⁵² Serup et al. have found that none of the women with White classes B or C (no evidence of retinopathy) developed persistent retinopathy as a consequence of pregnancy, while deterioration was noticed in 50% of the women with preexisting retinopathy. Additional support to the role of the severity of retinopathy as a risk factor for progression during pregnancy comes from a retrospective study of 23 pregnant diabetic women.¹⁴⁹ While none of the women with either no evidence of retinopathy ($n = 10$) or nonproliferative retinopathy ($n = 8$) experienced progression of retinopathy during pregnancy, four of the five women with proliferative retinopathy required photocoagulation during pregnancy due to the progression of retinopathy.

In a prospective study of 234 intensively treated pregnant diabetics,¹⁴⁶ Jervell et al. reported that the development or progression retinopathy occurred in 68 women (29%). Nevertheless, progression was rarely associated with loss of visual acuity.

In order to quantify the effect of pregnancy on diabetic retinopathy, Soubrane et al. followed 22 pregnant diabetics using serial fluorescein angiography examinations.¹⁵⁰ The mean number of microaneurysms increased from 42.7 before pregnancy to 56.7 at the 28th week and to 79.7 at the 35th week. This number decreased to 62.7 and 60.3 at 6 and 15 months postpartum, respectively. Similarly, Hellstedt et al.¹⁵⁶ followed the number of microaneurysms in 21 diabetic women with mild retinopathy. Microaneurysms were assessed during pregnancy and at 3 and 6 months postpartum using red-free photographs. The number of microaneurysms increased progressively during pregnancy and peaked at 3 months postpartum. This increase was related to the degree of improvement in glycemic control.

Phelps et al.¹⁵¹ prospectively studied 35 pregnant women with type 1 diabetes under tight glycemic control. The progression of nonproliferative retinopathy, noticed in 55% of the women, correlated with the levels of plasma glucose at entry and with the magnitude of improvement in glycemic control.

Klein et al.¹⁵³ assessed the effect of pregnancy on diabetic retinopathy using a control group of nonpregnant women with type 1 diabetes. In addition to poor glycemic control, pregnancy per se was a significant and independent risk factor for progression of retinopathy.

Rosenn et al.¹⁵⁴ reported a progression rate of 33% in a prospective study of 154 pregnant women with type 1 diabetes. They have found that hypertension, either chronic or pregnancy induced (PIH), was a significant and independent risk factor for the progression of retinopathy. The level of glycemic control and improved glycemic control in early pregnancy was also associated with the progression of retinopathy.

In the Diabetes in Early Pregnancy Study,¹⁵⁵ the risk of progression was strongly correlated with the severity of retinopathy before pregnancy. Thus, progression of more than two steps was noted in 10.3%, 21.1%, 18.8%, and 54.8% of the women with no, minimal (microaneurysms only), mild, and moderate-to-severe retinopathy at baseline, respectively. Progression to proliferative retinopathy was observed in 6.3% and 29% of the women with mild and moderate-to-severe retinopathy, respectively. Other factors associated with the progression of retinopathy included elevated baseline glycosylated hemoglobin and the magnitude of improvement of glycemic control in early pregnancy.

In another prospective study,⁸ 65 diabetic women were followed during pregnancy and 12 months postpartum. While the overall progression rate was 77.5%, only 26% of the women with no retinopathy at baseline had evidence of retinopathy during pregnancy. Duration of diabetes, poor glycemic control, anemia, and elevated systolic blood pressure were also risk factors for progression of retinopathy.

Lovestam et al.¹⁶¹ retrospectively compared a group of 65 pregnant women with type 1 diabetes with a matched group of nonpregnant women.

They have found preeclampsia to be a potent independent risk factor for progression of retinopathy. Moreover, Gordin et al.¹⁶⁴ have recently investigated the long-term impact of preeclampsia and PIH complicating pregnancies of 158 women with type 1 diabetes. Based on a follow-up of 16 years on average, preeclampsia and PIH were found to be independently associated with an increased risk of developing severe diabetic retinopathy later in life, with a hazard ratio of 3.5 and 3.2, respectively.

More recently, Vestgaard et al.¹⁵⁸ reported on the rate of progression of diabetic retinopathy in a prospective study of 102 pregnant women with type 1 diabetes who were managed by tight glycemic. Overall, progression of retinopathy occurred in 28 (27%) women. Sight-threatening progression occurred in six women and was associated with the presence of macular edema, impaired visual acuity, and higher blood pressure in early pregnancy, but not with HbA1c, decline in HbA1c, or prevalence of severe hypoglycemia.

While most of the data come from patients with type 1 diabetes, there is more recent evidence that pregnancy can affect the progression of diabetic retinopathy also in women with type 2 diabetes. In a recent study, Rasmussen et al.¹⁵⁷ studied the progression of diabetic retinopathy during pregnancy in 80 women with type 2 diabetes, 11 of whom had evidence of retinopathy in early pregnancy. The progression of retinopathy was observed in 11 (14%) women, and although it was mild in most cases, one case was complicated by progression from mild retinopathy to sight-threatening retinopathy and impaired vision in both eyes. Risk factors for the progression of retinopathy were a longer duration of diabetes and insulin treatment before pregnancy.

Studies not supporting a significant effect of pregnancy on progression of retinopathy

There are several studies that failed to demonstrate a significant effect of pregnancy on the natural history of diabetic retinopathy. Other studies have found that although retinopathy progressed during pregnancy, complete or partial regression was observed after delivery.

Stephens et al.¹⁵⁹ found the rate of development of retinopathy during pregnancy to be as low as 2%. Horvat et al.,¹⁶⁰ in a prospective study extending over 12 years, followed 172 diabetic women during pregnancy. Of the 40 women with nonproliferative retinopathy, only 4 (10%) progressed to proliferative retinopathy. They have found retinopathy to fluctuate during pregnancies, with simultaneous progression and regression of retinopathy in different parts of the same eye. Their conclusion was that pregnancy is not associated with an increased risk for progression of retinopathy and visual loss.

In another retrospective study,¹⁶¹ the progression of retinopathy in 65 pregnant women with type 1 diabetes was compared to a matched control group of 56 nonpregnant women with type 1 diabetes. The rate of sight-threatening deterioration of retinopathy was similar for the two groups (13% and 11%, respectively). Similarly, Temple et al. prospectively studied 179 pregnancies of women with type 1 diabetes.¹⁶³ The overall rate of progression of retinopathy during pregnancy was only 5%, and the rate of progression to proliferative retinopathy necessitating laser therapy was 2.2%.

In the DCCT,¹⁶² although pregnancy was associated with a greater risk for worsening of retinopathy, this worsening was transient, and the long-term risk for progression of retinopathy did not appear to be increased by pregnancy.

Some of the studies cited earlier have reported partial or complete regression of the pregnancy-related worsening of retinopathy. Moloney et al.¹⁴⁸ reported that by 6 months postpartum, the nonproliferative changes had regressed to control levels, and neovascularization showed some regression. Similarly, Serup et al.¹⁵² reported that postpartum regression was common and that proliferative changes that developed during pregnancy disappeared spontaneously after delivery in most of the cases. For that reason, the authors recommended that treatment with

photocoagulation during pregnancy and in the early postpartum period should be restricted. In the study of Rosenn et al.,¹⁵⁴ postpartum regression was observed in 13 of the 51 women (25%) in whom progression of retinopathy occurred during pregnancy. In a more recent study, Arun et al.¹⁶⁵ followed 59 women with type 1 diabetes for 5–10 years postpregnancy. Although four women required laser therapy during pregnancy, none of the women required laser therapy over the 5 years postpregnancy, although retinopathy was worsened in 14 women. On 10-year follow-up, only 1 of 22 women required laser therapy. The authors' conclusion was that pregnancy is not associated with significant postpartum worsening of retinopathy.

Suggested mechanism

Several mechanisms have been suggested by which pregnancy may lead to progression of retinopathy.

Pregnancy is associated with a dramatic change in the hormonal milieu. Human placental lactogen (hPL) is produced in enormous amounts by the placenta, reaching a production rate of about 1 g/day at term. Due to its GH-like activity, hPL may play an important role in the effect of pregnancy on diabetic retinopathy, as mentioned earlier.^{66,67,69} The vascular changes induced by the elevated levels of estrogen and progesterone during pregnancy may also contribute to the progression of retinopathy.

Pregnancy is also associated with marked physiological changes. The pregnancy-induced increase in cardiac output may lead to increased RBF, which could damage diabetic vessels. Chen et al. studied the changes in RBF during pregnancy in diabetic and nondiabetic women using laser Doppler velocimetry.¹⁶⁶ Among the diabetic women, only those whose retinopathy progressed had a significant increase in RBF during pregnancy. However, as these patients also had worse glycemic control (higher glycosylated hemoglobin levels prior to and throughout pregnancy), it is not clear if the deterioration can be attributed to the increase in RBF alone.

As mentioned earlier, hypertension is a risk factor for the progression of diabetic retinopathy.^{11,14,16,20,21,154} Hypertensive disorders are common in diabetic pregnancies, complicating up to 40% of pregnancies in women with type 1 diabetes.¹⁶⁷ Thus, hypertension may contribute to the progression of retinopathy during pregnancy.

Another possible mechanism is the improved glycemic control achieved by most of the diabetic women before or at the onset of pregnancy. As discussed earlier, rapid normalization of blood glucose is associated with the progression of retinopathy in both nonpregnant^{94–97} and pregnant^{151,154–156} patients.

In a recent study, Ringholm et al.¹⁶⁸ measured blood IGF-I levels in 88 women with type 1 diabetes at different time points along pregnancy. Overall, 22 (25%) women had evidence of new onset or progression of retinopathy. Although IGF-I levels increased throughout pregnancy in all women, the increase was significantly more rapid in women in whom retinopathy progressed. Elevated IGF-I level was independently associated with an increase in the

Table 54.3 Risk factors for progression of retinopathy during pregnancy

Risk factor	References
<i>Nonmodifiable</i>	
Duration of diabetes	[8,147,148]
Severity of retinopathy before conception	[147,152,155]
Poor glycemic control before conception	[8,151,154,155]
<i>Modifiable</i>	
Chronic or pregnancy-induced hypertension	[8,154,161]
Rapid normalization of blood glucose values	[151,154–156]
Anemia	[8]

risk of progression of retinopathy (odds ratio 2.0, 95% confidence interval 1.1–3.6).

Finally, it has been recently hypothesized that pregnancy-induced changes in the immune system may contribute to the progression of retinopathy during pregnancy.¹⁶⁹ These changes, which have been previously implicated in the pathogenesis of diabetic retinopathy, include generalized leukocyte activation and upregulation of adhesion molecules that may lead to leukocyte–endothelial interaction and the consequent leukostasis with capillary occlusion, ischemia, and vascular leakage. In addition, pregnancy is associated with an increase in the levels of certain cytokines that are known to cause blood–retina barrier breakdown and to promote angiogenic and proliferation and thereby contribute to progression of retinopathy.

Summary

In summary, it appears that pregnancy is associated with the progression of diabetic retinopathy and that the risk for progression is related to the factors presented in Table 54.3. One major drawback of many of these studies presented earlier is the lack of a matched control group of nonpregnant diabetic women. The progression of retinopathy during pregnancy may be the result of the normal hormonal and physiological changes during pregnancy as well as the improved glycemic control and high rate of hypertensive disorders observed in diabetic pregnancies. Nevertheless, these changes may regress postpartum, especially in cases of nonproliferative retinopathy, and may not affect the long-term progression of retinopathy.¹⁶²

Diabetic retinopathy and perinatal outcome

Several investigators have addressed the issue of a possible relationship between diabetic retinopathy and perinatal outcome. Moloney et al.¹⁴⁸ noted that maternal retinal hemorrhages or neovascularization was associated with increased infant morbidity. McElvy et al.¹⁷⁰ performed a prospective study of 205 pregnant women with type 1 diabetes. The development or progression of retinopathy during

pregnancy was significantly associated with reduced fetal growth, manifested by lower mean birth weight and a higher rate of small-for-gestational-age (SGA) and low birth weight infants. There was no correlation between progression of retinopathy and gestational age at delivery, preterm delivery, respiratory distress syndrome, neonatal hypoglycemia, or neonatal death.

Klein et al.¹⁷¹ reported adverse perinatal outcome in 33 of 179 diabetic pregnancies. Severity of retinopathy was the only variable that significantly predicted adverse perinatal outcome. Lauszus et al.¹⁷² reviewed the records of 26 diabetic pregnancies with preexisting proliferative retinopathy. Proliferative retinopathy was associated with increased preterm delivery rate (27%) and serious neonatal morbidity.

Management of diabetic retinopathy during pregnancy

As discussed earlier, diabetic retinopathy can worsen during pregnancy. Thus, patients with diabetic retinopathy should undergo preconception counseling and follow-up during pregnancy by a multidisciplinary team that includes a perinatologist, endocrinologist, and ophthalmologist that are experienced in the management of diabetic retinopathy.

Preconception counseling

Patients with diabetes who are planning to become pregnant should be given a thorough explanation on the risk of the development or progression of diabetic retinopathy during pregnancy and the importance of glycemic control throughout pregnancy. Patients with high-risk characteristics (long-standing diabetes, severe retinopathy, coexisting hypertension, poor glycemic control) should be identified and followed appropriately.

A comprehensive eye examination prior to conception should be performed by an ophthalmologist experienced in the care of diabetic retinopathy. This examination carries great importance since it determines the risk for progression of retinopathy, the frequency of follow-up visits during pregnancy, and the need for laser photocoagulation prior to conception.

Glycemic control should be achieved prior to conception in order to reduce the risk of progression of retinopathy as well as to avoid the adverse maternal and fetal outcome associated with poorly controlled diabetes during pregnancy. One goal is to achieve a glycosylated hemoglobin level of less than six standard deviations above normal prior to conception.¹⁵⁵ In the presence of proliferative or severe nonproliferative retinopathy, normalization of blood glucose levels should be achieved gradually over a period of weeks to months in order to avoid progression of retinopathy that may result from rapid normalization. However, in patients presenting after conception, blood glucose should be normalized as soon as possible since the benefits of good glycemic control in early pregnancy far outweigh the risk of transient progression of retinopathy. Other risk factors, such as uncontrolled chronic hypertension, should be followed and treated adequately prior to conception.

One question that needs to be answered is the role of laser photocoagulation prior to conception. As discussed earlier, the ETDRS have found that in type 1 diabetes, panretinal

photocoagulation is beneficial mainly in cases of high-risk proliferative retinopathy and clinically significant macular edema. However, it is recommended that in cases of impending pregnancy, during which rapid progression of retinopathy may occur, photocoagulation should be instituted at earlier stages, as in cases of severe nonproliferative or early proliferative retinopathy.^{108,109} In one study of women with proliferative retinopathy, treatment with laser photocoagulation before conception was associated with significant progression of retinopathy in 26% of the women compared with 58% when treatment was initiated in early pregnancy.¹⁷³

Antenatal follow-up

The concerns regarding rapid optimization of glycemic control with respect to progression of retinopathy in diabetic women with poor glycemic control who did not have preconception counseling have been described earlier. Nevertheless, according to the 2008 National Institute for Health and Care Excellence (NICE) guidelines, diabetic retinopathy should not be considered a contraindication to rapid optimization of glycemic control in women who present with a high HbA1c in early pregnancy.¹⁷⁴

The frequency of eye examinations during pregnancy depends on the severity of retinopathy prior to conception, evidence of progression of retinopathy, glycemic control, duration of diabetes, and the presence of other risk factors such as hypertension. Thus, patients with no or minimal retinopathy should be evaluated in the first and third trimesters.¹⁷⁴ Patients with mild to moderate retinopathy should undergo evaluation each trimester. In cases of severe nonproliferative or proliferative retinopathy, when there is evidence of progression of retinopathy, and in patients with poor glycemic control or hypertension, follow-up may be needed every 2–4 weeks.^{153,155,162,175,176}

Fluorescein angiography is a sensitive tool to assess the extent of capillary nonperfusion and early neovascularization and may aid in guiding treatment of macular edema, although ophthalmoscopic examination is satisfying in most of the cases for the diagnosis of proliferative retinopathy. In addition, although detrimental effects of fluorescein dye on the fetus have not been documented,¹⁷⁷ fluorescein does cross the placenta into the fetal circulation. Thus, fluorescein angiography during pregnancy is generally not indicated.

Laser photocoagulation during pregnancy

The use of laser photocoagulation during pregnancy is controversial. In general, the indications for treatment and the response to laser photocoagulation are the same as for nonpregnant women.^{178,179} As described earlier, several studies reported that postpartum regression of the pregnancy-induced progression of retinopathy is common,^{148,152} and the authors recommended that treatment with photocoagulation during pregnancy and in the early postpartum period should be restricted. In contrast, others believe that because the progression of retinopathy during pregnancy can be at times rapid and aggressive, treatment with laser photocoagulation should be applied during pregnancy and after delivery when indicated.^{147,180,181}

Thus, the decision whether to treat should be made on an individual basis, taking into account the severity of retinopathy, evidence of progression, lack of glycemic control, the presence of additional risk factors, and, on the other hand, the risks and side effects associated with laser photocoagulation.

According to the ETDRS,¹⁸² in patients with DME, focal photocoagulation should be performed during pregnancy, because spontaneous regression rarely occurs after delivery. If the edema does not respond well to photocoagulation, hospitalization is required, with diuretic treatment and occasionally steroids.¹⁸³

Insulin analogues during pregnancy and diabetic retinopathy

In addition to its metabolic effects that are mediated by the insulin receptor, insulin also has a mitogenic effect, currently thought to be mediated by the IGF-1 receptor. The possible role of IGF-1 in the pathogenesis of diabetic retinopathy (discussed earlier) and the change in the relative affinity of the insulin analogues toward the IGF-1 receptor have raised concerns regarding the effect of these analogues on diabetic retinopathy.

Insulin lispro has a 1.5-fold higher affinity toward the IGF-1 receptor compared with human insulin, and the initial suggestion that insulin lispro may worsen retinopathy was made by Kitzmiller et al.¹⁸⁴ In this study, of the ten patients who were treated with insulin lispro and had no evidence of retinopathy prior to conception, three developed bilateral proliferative changes, and two developed VH during pregnancy. However, these patients had poor glycemic control at baseline and experienced significant improvement in glycemic control during pregnancy, two major risk factors that may be responsible for the progression of retinopathy in these cases. Subsequent studies did not support an effect of insulin lispro on retinopathy.^{185–188} Insulin aspart is similar to insulin lispro in many aspects, although its affinity to the IGF-1 receptor is the same as human insulin.¹⁸⁹ There are only little data on insulin aspart in pregnancy, and currently it remains a category C medication for pregnancy.¹⁸⁵ The results of multicentric study now in progress on the efficacy and safety of insulin aspart in pregnant patients with type 1 diabetes will provide important information on the safety of insulin aspart during pregnancy.¹⁹⁰ Insulin glargine has a higher affinity to IGF-1 receptor and a greater mitogenic activity compared with human insulin (6.5-fold and

Preconception counseling

- *Patient education*—Explanation on the risk of development or progression of diabetic retinopathy during pregnancy, and the importance of glycemic control during pregnancy.
- *Risk stratification*—Identification of patients with high-risk characteristics
- *Comprehensive eye examination*
- *Improve of glycemic control*—Should be achieved gradually, especially in patients with advanced retinopathy.
- *Control of co-existing hypertension*
- *Laser photocoagulation* should be considered in patients with severe non-proliferative or proliferative retinopathy

Antenatal care

- *Multidisciplinary team*—Perinatologist, endocrinologist and ophthalmologist that are experienced in the management of diabetic retinopathy.
- *Frequency of eye examinations:*

No—Minimal retinopathy	1st, 3rd trimesters
Mild—Moderate retinopathy	1st, 2nd, 3rd trimesters
Severe NPDR, PDR	
Evidence of progression	Every 2–4 weeks
Poor glycemic control	
Other risk factors	
- *Fluorescein angiography* is usually avoided during pregnancy
- *Laser photocoagulation*—Because postpartum regression is common, laser photocoagulation should be considered in cases severe non-proliferative or proliferative retinopathy on an individual basis considering the severity of retinopathy, evidence of progression, lack of glycemic control, and the presence of additional risk factors.
- *Macular edema* should be treated with focal laser photocoagulation, diuretics, or steroids.

Delivery

- There is no need for labor induction in women with good glycemic control.
- In cases of high-risk proliferative retinopathy, *elective cesarean section or shortening of the second stage* should be considered due to the risk of vitreous hemorrhage.

Figure 54.4 Recommendations for the management of pregnancies complicated by diabetic retinopathy.

8-fold, respectively),¹⁸⁹ which raised concerns on its effects in diabetic retinopathy. Two randomized trials demonstrated an increased risk of progression of retinopathy¹⁹¹ and a higher incidence of new onset macular edema.¹⁹² However, there was lack of consistency between the methods of assessment, and subsequent prospective randomized studies did not support these observations. A large 5-year randomized multicenter study is in progress.¹⁸⁵ For the moment, the use of insulin glargine during pregnancy is not recommended. The affinity of insulin detemir to IGF-I receptor is fivefold lower than human insulin, and its mitogenic activity is reduced by tenfold.¹⁸⁹ There are no data on the use of insulin detemir in pregnancy.

Delivery

Earlier studies recommended early delivery, as soon as lung maturation was achieved, in pregnancies complicated by retinopathy and other vascular diseases. However, more recent research has shown that a well-controlled diabetic pregnancy can be allowed to continue to term in order to avoid iatrogenic prematurity, the risk of amniocentesis, failed induction of labor due to unfavorable cervix, and unnecessary cesarean section.¹⁹³

The Valsalva maneuver during labor might induce VH from active neovascularization.^{194,195} The role of elective cesarean section in these cases is controversial. The mode of delivery should be discussed in advance between the patient and obstetrician. According to the 2008 NICE guidelines, diabetic retinopathy should not be considered a contraindication to vaginal birth.¹⁷⁴ A summary of recommendations for management is presented in Figure 54.4.

Summary

Diabetic retinopathy is the most common chronic complication of diabetes mellitus, and it is estimated that 20%–30% of diabetic women in the reproductive age group has some evidence of retinopathy.

The purpose of this chapter was to review the current literature on the effects of pregnancy on diabetic retinopathy and to provide guidelines for the management of pregnancies complicated by diabetic retinopathy.

It appears that pregnancy is associated with the progression of diabetic retinopathy, especially in women with the risk factors presented in Table 54.3, although these changes may regress postpartum, especially in cases of nonproliferative retinopathy, and may not affect the long-term progression of retinopathy. In addition, the presence of diabetic retinopathy is associated with adverse pregnancy outcome, including fetal growth restriction, and preterm delivery.

Patients with diabetic retinopathy should undergo preconception counseling and follow-up during pregnancy by a multidisciplinary team as summarized in Figure 54.4. It is now clear that White's advice at 1971 to terminate pregnancies in diabetic patients with progressive proliferative retinopathy is no longer valid¹⁹⁶ and that with careful professional care, a favorable pregnancy outcome can usually be expected with minimal or no deterioration in ophthalmologic status. Ongoing trials may provide better answers regarding the use of laser photocoagulation and the safety of insulin analogues during pregnancy.

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Introduction

By the end of the last century, diabetic nephropathy was present in up to 7% among unselected pregnant women with type 1 diabetes, but in a recent study, it was reported that the prevalence of diabetic nephropathy is now 2.5% and 2.3% in pregnancies complicated by type 1 and type 2 diabetes, respectively. In line with this, the current prevalence of microalbuminuria is now 3.4% and 4.5%, respectively.^{1,2}

For many years, pregnancy in women with diabetic nephropathy was associated with a very high risk of severe pregnancy complications including perinatal mortality as well as deterioration of maternal kidney function leading to end-stage renal disease.^{3,4} However, maternal and perinatal mortality and morbidity rates in pregnancies complicated by diabetic nephropathy have declined substantially during the last decade. Successful pregnancy outcome with fetal survival rates of up to 95%–100% is now the norm in developed countries.^{5–12} Nonetheless, maternal and perinatal complications in pregnancies of women with diabetic nephropathy are often related to elevated blood pressure and are still more common than in diabetic women with normal urinary albumin excretion at conception.^{2,4}

The present chapter highlights factors of importance for the clinical care of pregnant women with diabetic nephropathy or microalbuminuria with particular focus on the possible role of strict antihypertensive treatment during pregnancy. The majority of data on this topic are from women with type 1 diabetes. Most likely the findings are similar in women with type 2 diabetes, and the clinical recommendations given in this chapter are probably useful in both types of diabetes.

Pathophysiology and treatment of diabetic nephropathy outside of pregnancy

Diabetic nephropathy is a progressive disease that affects approximately 30% of patients with diabetes and is the most common cause of end-stage renal disease in the United States. In Denmark, 22% of patients with end-stage kidney disease have diabetes.¹³ The first clinical sign is microalbuminuria,

defined as a urinary albumin excretion of 30–300 mg/24 h, corresponding to a spot urine albumin to creatinine ratio of 30–300 µg/mg. Left untreated, microalbuminuria tends to progress to overt diabetic nephropathy characterized by persistent proteinuria, hypertension, and a relentless decline in glomerular filtration rate.¹⁴ Histological changes in the glomeruli with increased basal membrane thickness and glomerulosclerosis are characteristic. Elevated blood pressure is a marker of poor prognosis and is associated with progression of the kidney disease. If left untreated, progression to end-stage renal disease occurs within a median of 7 years after onset of diabetic nephropathy. Meanwhile, progression of diabetic nephropathy can be slowed by the use of strict antihypertensive treatment including renin–angiotensin system inhibition in terms of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists as first-line drugs. Accordingly, the prognosis has improved considerably.^{4,15–17} It is often necessary to combine this treatment with diuretics, beta-blockers, and/or calcium antagonists in order to control the blood pressure and the urinary albumin excretion sufficiently. Strict antihypertensive treatment in patients with diabetic nephropathy results in the preservation of kidney function documented by a reduction in the decline of glomerular filtration rate to less than one-third of the decline in untreated patients.¹⁸ Inhibition of the renin–angiotensin system in normotensive patients with microalbuminuria may reduce and possibly eliminate albuminuria in patients with type 1 diabetes treated with ACE inhibitors^{18,19} as well as in patients with type 2 diabetes treated with angiotensin II receptor antagonists.²⁰ The treatment goal includes blood pressure below 130/80 mmHg²¹ and to lower or normalize urinary albumin excretion.

Renin–angiotensin system inhibition is, however, contraindicated in pregnancy, and alternative antihypertensive drugs tolerated in pregnancy must be used as discussed in the following text.

Pathophysiology of preeclampsia and hypertension in diabetic pregnancy

Preeclampsia is characterized by hypertension, proteinuria, and peripheral edema developing after 20 gestational weeks. Patients with diabetic nephropathy or microalbuminuria prior to pregnancy are at increased risk of developing

preeclampsia and may already present with elevated blood pressure in early pregnancy.²² Women with diabetes developing preeclampsia are generally characterized by higher urinary albumin excretion, blood pressure, and HbA1c in early pregnancy compared with women who do not develop preeclampsia.²³ Women with type 1 diabetes developing preeclampsia have impaired vasodilatory capacity present already in early pregnancy, several weeks prior to the clinical presentation of preeclampsia. In addition, the markers of endothelial dysfunction vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (I-CAM) are elevated in early pregnancy.²³ Signs of vascular dysfunction thus precede development of clinical preeclampsia in women with type 1 diabetes who are prone to the condition. In addition, several other pathophysiological aspects are involved such as increased oxidative stress and reduced antioxidative defenses that may be related to levels of vitamin C and E.^{24,25} However, supplementation with vitamin C and E in a randomized study including 762 women with type 1 diabetes did not reduce the risk of preeclampsia.²⁵ As in preeclampsia in women without diabetes, preeclampsia in women with type 1 diabetes is also associated with elevated levels of anti-angiogenic factors in the third trimester.²⁶

Preeclampsia and the renin–angiotensin system

During the early stages of normal pregnancy, activation of the local^{27,28} and systemic^{29,30} renin–angiotensin systems is present. At 3–6 gestational weeks, the plasma prorenin level increases tenfold, with a much lower prorenin level from 9 weeks onward.²⁷ This is consistent with the role of the renin–angiotensin system, particularly prorenin, in embryonic and fetal development and in placentation.²⁷ In preeclampsia, disturbance in the renin–angiotensin system is seen with increased vascular responsiveness to angiotensin II.³¹ The prorenin levels in 108 pregnant women with type 1 diabetes have been prospectively investigated, and prorenin concentrations at 8 gestational weeks were positively associated with later development of preeclampsia.³² Likewise, throughout pregnancy, prorenin concentrations were 30% higher in the nine women with type 1 diabetes who developed preeclampsia compared to those who did not.³²

Preeclampsia and vasoactive markers

The vasoactive marker of cardiac overload, atrial natriuretic peptide (ANP), is synthesized in cardiac tissue in response to volume expansion and ventricular pressure overload.^{33,34} In nondiabetic women, increased levels of ANP and brain natriuretic protein (BNP) are seen in late pregnancy when the diagnosis of preeclampsia has been established.^{35,36} In a small, prospective series of women with type 1 diabetes followed throughout pregnancy, preeclampsia developed in six women (7%) with significantly higher ANP levels at

nine gestational weeks as compared with women not developing preeclampsia. Throughout pregnancy, ANP levels were 34% higher in these women.³⁷ However, the function of placenta in the early stage of pregnancy judged by the level of activin A and inhibin A is often well preserved in diabetic women developing preeclampsia.³⁸ Similarly, growth restriction of the fetus is rare in diabetic women with preeclampsia.³⁸

Pathogenesis of preeclampsia in women with diabetes and nephropathy

We suggest that the increased prevalence of preeclampsia in women with type 1 diabetes complicated with diabetic nephropathy or microalbuminuria is mainly related to common maternal constitutional factors with an increased susceptibility to endothelial dysfunction. The pathogenesis of development of preeclampsia in women with diabetic nephropathy or microalbuminuria and type 1 diabetes does thus include presence of endothelial dysfunction,²³ impaired maximal vasodilatation,²³ increased levels of components of the renin–angiotensin system,³² and markers of cardiac overload.³⁷ All these can be modulated by antihypertensive treatment. Thus, tight antihypertensive treatment during pregnancy to prevent increase in blood pressure and/or urinary albumin excretion theoretically should be beneficial in these women.

Effect of diabetic nephropathy on pregnancy outcome

Diabetic nephropathy may adversely affect the outcome of pregnancy mainly by three mechanisms: (1) preterm delivery due to maternal hypertensive complications, (2) fetal intrauterine growth restriction and fetal distress caused by placental dysfunction, or (3) deterioration of maternal kidney function. In addition, congenital malformations have been described with a slightly higher prevalence in women with diabetic nephropathy compared to diabetic women with normal kidney function.³⁹

The prevalence of preeclampsia in women with diabetic nephropathy is up to 64%^{4,5,7,12} especially in the presence of reduced kidney function,⁴⁰ hypertension at the start of pregnancy, or nephrotic proteinuria.^{5,7} Also, women with type 1 diabetes and microalbuminuria are at increased risk of developing preeclampsia compared to women with type 1 diabetes and normal urinary albumin excretion,^{26,41} and these women are also at particular risk of preterm delivery⁴¹ where preterm delivery before 34 gestational weeks has been reported in up to 45%.^{9,41} Severe disabilities of the children born to mothers with diabetic nephropathy have also been described. In a follow-up study of 35 children born between 1982 and 1992 by women with diabetic nephropathy, the majority were developmentally normal, but neurodevelopmental problems were seen in children born preterm with a

birth weight less than 2000 g.⁹ The risk of perinatal mortality in pregnancies complicated by diabetic nephropathy is now close to that of women with type 1 diabetes without diabetic nephropathy.^{2,4,5,7,12} Recently, similar pregnancy outcomes were reported in women with kidney involvement and either type 1 or type 2 diabetes.¹

Effects of pregnancy on diabetic nephropathy

Only a few studies have addressed the long-term impact of pregnancy on renal function in women with diabetic nephropathy. The most recent study is a prospective cohort study including women with diabetic nephropathy, and normal serum creatinine offered strict blood pressure control during the whole follow-up period of 16 years. In total, 26 women had at least one pregnancy during the period and 67 had no pregnancies in the observation period. In these women with normal serum creatinine, pregnancy was not associated with a greater decline in kidney function or impaired long-term maternal survival.⁴² However, other studies report that in women with a reduced creatinine clearance before pregnancy, there is increased risk of deterioration of kidney function during pregnancy.^{6,22,43}

In general, pregnancy outcome is favorable in women with small elevations in serum creatinine, i.e., less than 124 $\mu\text{mol/L}$ (1.4 mg/dL), with proteinuria less than 1 g/24 h, and with normal blood pressure.⁴⁴ In contrast, serum creatinine above 176 $\mu\text{mol/L}$ and severe hypertension or proteinuria in the nephrotic range (>3 g/24 h) and/or preexisting cardiovascular disease are associated with a high risk for poor maternal and fetal outcome.⁴⁴ The long-term survival of a mother with diabetic nephropathy has improved considerably in recent years, but the long-term likelihood of complications including visual impairment and renal dysfunction is still increased.^{4,9,11,42}

Prepregnancy counseling of women with diabetic nephropathy

Careful counseling of the woman with diabetes and kidney involvement concerning the risk for herself and the newborn is important for a well-considered decision regarding pregnancy. The use of safe contraception in the planning phase is recommended.⁴⁵

To minimize the risk of pregnancy-induced maternal progression to end-stage renal failure, focusing on the prepregnancy level of serum creatinine is important, since serum creatinine above 176 $\mu\text{mol/L}$ is the best predictor of the risk of pregnancy-induced decline in maternal kidney function leading to end-stage renal disease during pregnancy or shortly after.⁴⁴ In addition, an updated diabetes status including self-monitored glucose values, HbA1c, risk of severe hypoglycemia, degree of diabetic retinopathy, serum

creatinine, blood pressure, and proteinuria is necessary to estimate the risk for complications during pregnancy in a woman with diabetic nephropathy. Smoking and alcohol consumption are discouraged strongly during pregnancy. Both the level of blood pressure and the actual number of antihypertensive agents used to control the blood pressure sufficiently prior to pregnancy are of importance to predict and plan the need for further intensification of antihypertensive treatment during pregnancy.

Glycemic control

Poor glycemic control before pregnancy is associated with pregnancy complications such as congenital malformations,^{46,47} preeclampsia,^{48–50} and preterm delivery.⁴⁶ Strict glycemic control is therefore the goal, and HbA1c as close to normal as possible at least below 7% is recommended. The risk of severe hypoglycemia has to be taken into account.⁵¹

Low-dose aspirin

Low-dose aspirin treatment is indicated in women with diabetic nephropathy or microalbuminuria to prevent cardiovascular events, and it might also prevent preeclampsia.⁵² If a woman is already on low-dose aspirin treatment before pregnancy, this treatment may be continued, while initiation of low-dose aspirin treatment in pregnancy normally is postponed until after organogenesis (10–12 weeks).

Folic acid

Daily folic acid supplementation should be advised as it might reduce the risk of fetal malformations.⁵³ There is no consensus on the dose of folic acid; at least 400 $\mu\text{g/day}$ is recommended in Denmark, while in Canada and the United States, the recommendation is up to 5 mg/day.⁵⁴

Blood pressure control

Prepregnancy treatment with ACE inhibitors combined with strict metabolic control for at least 6 months resulting in low levels of urinary albumin excretion has been found to be associated with a high rate of successful pregnancy outcome.⁵

Whether treatment with ACE inhibitors or angiotensin II receptor antagonists in early pregnancy is associated with increased risk of congenital malformations is currently being debated.^{39,55–57} However, treatment with ACE inhibitors during the last part of pregnancy is associated with abnormal fetal renal development and neonatal renal failure.^{55,58} Treatment with ACE inhibitors or angiotensin II receptor antagonists should therefore ideally be stopped prior to conception,^{55,58} but if these drugs are given during organogenesis, interruption of pregnancy is not indicated on this background.⁵⁶ If the severity of diabetic nephropathy indicates continuous treatment with inhibitors of the renin-angiotensin system, in the case of unplanned pregnancy, a shift to other antihypertensive agents can successfully take

place in early pregnancy when the pregnancy test is positive.⁵ Types of antihypertensive agents that are considered safe in pregnancy are methyldopa, beta-blockers (such as labetalol), and the calcium antagonists nifedipine and diltiazem.⁴ Although the use of diuretics throughout pregnancy is controversial,⁵⁹ we have good clinical experience with continuation of diuretic treatment initiated before pregnancy in stable doses during pregnancy in women with diabetic nephropathy.^{4,60}

Cholesterol-lowering drugs

Treatment with statins or other cholesterol-lowering agents during pregnancy may be associated with malformations or changes in the development of the central nervous system and should ideally be discontinued prior to pregnancy⁶¹ or as soon as pregnancy is diagnosed.

Diabetic retinopathy

Sight-threatening diabetic retinopathy is prevalent in women with diabetic nephropathy, and it is well known that a pregnancy-induced deterioration of retinopathy may occur. Treatment for diabetic retinopathy should therefore be performed if indicated to stabilize the retinopathy prior to pregnancy.^{62,63}

Summary of prepregnancy care

Intensive glycemic control, folic acid supplementation, and intensive antihypertensive treatment are of importance prior to pregnancy in women with diabetic nephropathy or microalbuminuria. Renin-angiotensin system inhibitors and cholesterol-lowering agents should ideally be stopped before pregnancy or at the latest when pregnancy is diagnosed. Screening for diabetic retinopathy and treatment, if indicated, is important (Table 55.1).

Table 55.1 Prepregnancy counseling of women with diabetic nephropathy

- Use of safe contraception in the planning phase
- Evaluation of the risk of pregnancy-induced maternal kidney failure
- Evaluation of the risk of preeclampsia and preterm delivery
- Intensive glycemic control with HbA1c as near to normal levels as possible (<7%, ~50 mmol/mol)
- Supplementation with folic acid
- Tight target for antihypertensive treatment, i.e., BP <130/80 mmHg and urinary albumin excretion <300 mg/24 h
- Consider change to pregnancy-friendly antihypertensive agents before conception
- Review the medication list for drugs contraindicated in pregnancy, i.e., cholesterol-lowering agents
- Screen for sight-threatening diabetic retinopathy

Treatment of women with diabetic nephropathy during pregnancy

Glycemic control

Strict glycemic control during pregnancy is of utmost importance but may be difficult because pregnant women with type 1 diabetes have an increased risk of severe hypoglycemia, particularly in early pregnancy.⁵¹ Development of preeclampsia is more frequent in women with higher levels of HbA1c in early pregnancy,^{48–50} but it is reassuring that improvement of glycemic control during pregnancy is associated with less preeclampsia.⁶⁴ The British NICE guidelines recommend HbA1c below 6.0% during pregnancy.⁶⁵

Low-dose aspirin

In women with high risk of developing preeclampsia, treatment with low-dose aspirin has some preventive effect⁵² if initiated before 16 gestational weeks. It is not known what is the optimal gestational age to start low-dose aspirin, but generally it is initiated after the organogenesis. Low-dose aspirin treatment in women with diabetic nephropathy is therefore recommended in American⁶⁶ and British⁶⁵ guidelines. The British NICE guidelines now recommend 75 mg aspirin daily from 12 gestational weeks to all pregnant women with diabetes and/or kidney disease.⁶⁵ Preferably this treatment should be stopped 1 week before delivery, i.e., at 36–37 weeks.

Folic acid

Daily folic acid supplementation during the first 12 gestational weeks might reduce the incidence of congenital malformations in pregnant women with diabetes.⁵³

Blood pressure control

A gradual increase in both blood pressure and urinary albumin excretion has been demonstrated prior to onset of preeclampsia in women with type 1 diabetes.⁴⁸ With the aim to reduce the high prevalence of preeclampsia in pregnant women with diabetic nephropathy or microalbuminuria, our group in the year 2000 decided to initiate antihypertensive treatment if blood pressure exceeded 140/90 mmHg or urinary albumin excretion exceeded 2000 mg/24 h. If the women already were on antihypertensive treatment, the drugs were changed to antihypertensive agents well tolerated in pregnancy such as methyldopa, labetalol, or nifedipine. In an unselected cohort of 20 normotensive pregnant women with type 1 diabetes and microalbuminuria treated according to this strategy, a significant reduction in preterm delivery before 34 gestational weeks was seen when compared to a previous cohort where antihypertensive treatment for elevated blood pressure was less rigorous.⁶⁰ However, the prevalence of preeclampsia and preterm delivery was still high, and therefore, we decided in 2004 to intensify the strategy even more by initiating antihypertensive treatment

when blood pressure exceeds 135/85 mmHg or urinary albumin excretion exceeds 300 mg/24 h. This strategy seems to be associated with further improvement as fewer women with type 1 diabetes and microalbuminuria developed preeclampsia or delivered preterm in the following audit.²

Furthermore, in women with diabetic nephropathy, early-onset and intensive antihypertensive treatment most likely also reduces the severity of preeclampsia and preterm delivery.^{1,2,4} It is often necessary to use a combination of different antihypertensive agents to control blood pressure and urinary albumin excretion.⁴ Methyldopa, labetalol, nifedipine, and diltiazem are often used and are apparently safe in pregnancy.^{4,60,67} In addition, diuretics, both thiazides and loop diuretics, may be used with caution during pregnancy, and we often find it necessary to continue with unchanged dose of diuretics if the women are already treated with this class of drug prior to pregnancy due to diabetic nephropathy,^{4,60} while we normally do not use diuretics in other pregnant women. Many women with diabetic nephropathy can be controlled with one or two antihypertensive agents, but as many as four different antihypertensive classes of drugs, including diuretics, are used for selected pregnant women at our center in order to stabilize the blood pressure.^{2,4,60} Although antihypertensive agents have been reported to be associated with intrauterine growth restriction,⁶⁸ this seems not to be the case in women with diabetes.^{1,2}

Carr et al.⁶ described a cohort of 43 pregnant women with diabetic nephropathy where suboptimal control of hypertension in early pregnancy was associated with increased risk of preterm delivery compared to women with well-controlled blood pressure on medical treatment (38% vs. 5%).

Although prospective, randomized trials are not available, studies from our center^{1,2,60} in combination with studies by Kimmerle⁹ and Carr⁶ strongly suggest that women with diabetes and diabetic nephropathy or microalbuminuria receiving early and intensive antihypertensive treatment have a better pregnancy outcome compared to women initiating antihypertensive treatment in late pregnancy.

The mechanism of the effect of early and intensive antihypertensive treatment in pregnant women with diabetic nephropathy or microalbuminuria is not known. Antihypertensive treatment may stabilize the urinary albumin excretion and the universal leakage of albumin from the microcirculation and thus improve the endothelial function. Thereby, the antihypertensive treatment reduces not only blood pressure and urinary albumin excretion but also the other clinical manifestations of preeclampsia associated with maternal endothelial dysfunction. The beneficial effect of antihypertensive treatment of diabetic nephropathy or microalbuminuria in normotensive patients with type 1 diabetes outside pregnancy is well documented.¹⁴

Obstetric surveillance

In late pregnancy, close obstetrical surveillance including frequent ultrasound examinations of fetal growth and non-stress testing are important to diagnose complications and plan the time and mode of delivery.⁴⁵

Diabetic retinopathy

Besides protecting the kidney function, focusing on diabetic retinopathy is important in these women since progression to sight-threatening diabetic retinopathy is prevalent during pregnancy.^{62,63} Laser treatment should be performed during pregnancy, if indicated.⁶³

Summary of treatment recommendations

Strict glycemic control, low-dose aspirin, folic acid supplementation, and intensive antihypertensive treatment with pregnancy-friendly drugs are of importance during pregnancy in women with diabetic nephropathy or microalbuminuria. The goal for antihypertensive treatment includes both lowering of blood pressure and urinary albumin excretion and is stricter compared to pregnant women without diabetes. Close obstetric surveillance and screening for diabetic retinopathy is important to improve pregnancy outcomes in these high-risk pregnancies (Table 55.2).

Concluding remarks

Pregnancy outcome in women with diabetic nephropathy or microalbuminuria has improved considerably over the last decade with a take-home-baby rate of approximately 95%. Most information in the literature comes from women with type 1 diabetes and diabetic nephropathy or microalbuminuria, but the same numbers are probably also valid for women with type 2 diabetes. Careful counseling of women with diabetic nephropathy or microalbuminuria prior to pregnancy with estimation of the risk for the mother and fetus is important. Pregnancy does not result in worsening of kidney function in women with diabetic nephropathy and normal serum creatinine, but pregnancy complications are common.

Strict glycemic control before and during pregnancy, low-dose aspirin from 10 to 12 gestational weeks onward, folic acid supplementation in early pregnancy, and intensive antihypertensive treatment are important factors for optimizing pregnancy outcome. Methyldopa, labetalol, nifedipine, and diltiazem are regarded safe in pregnancy, whereas ACE inhibitors, angiotensin II receptor antagonists, or cholesterol-lowering agents should not be used during

Table 55.2 Treatment of women with diabetic nephropathy during pregnancy

- Intensive glycemic control
- Low-dose aspirin from 10–12 weeks until 36–37 weeks
- Supplementation with folic acid during the first 12 weeks
- Tight target for antihypertensive treatment, i.e., BP <135/85 and urinary albumin excretion <300 mg/24 h
- Use of pregnancy-friendly antihypertensive agents
- Review the medication list for drugs contraindicated in pregnancy, i.e., cholesterol-lowering agents
- Tight obstetric surveillance
- Screen for sight-threatening diabetic retinopathy

pregnancy. Case series and pathophysiological studies support a stringent goal for blood pressure and urinary albumin excretion in pregnant women with diabetic nephropathy or microalbuminuria. Screening for diabetic retinopathy

before and during pregnancy is mandatory, and laser treatment should be performed if indicated. Further research on the benefit and risk of intensive antihypertensive treatment in this population is needed.

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56 Diabetic ketoacidosis

Annunziata Lapolla and Maria Grazia Dalfrà

Diabetic ketoacidosis (DKA) is a serious complication of diabetes resulting often in a medical emergency. Nowadays, the occurrence of DKA is rare in pregnant women with diabetes, occurring mainly in patients with type 1 diabetes, but also in type 2 or, more rarely, in women with gestational diabetes mellitus (GDM). Maternal and fetal complications determined by DKA can be life threatening, so prompt recognition and treatment of this condition is mandatory to avoid these complications.

Incidence

The reported incidence of diabetes in pregnancy ranges from 6% to 7% with 90% of cases constituted by women affected by GDM.^{1,2} In this context, DKA has a reported incidence between 0.5% and 3% of all diabetic pregnancies.³⁻⁹ Previously considered typical of type 1 diabetes is now reported also to occur in patients with type 2 diabetes and GDM. Furthermore, the increase of the utilization of assisted reproductive technology resulting often in multifetal gestation can be a risk factor for the development of DKA; in fact, this gestation can be associated with preterm labor determining the necessity to utilize corticosteroid for fetal lung maturation, a therapy that in diabetes disease can determine hyperglycemia and subsequently DKA.

Pathophysiology

DKA is a complex metabolic disorder characterized by hyperglycemia, acidosis, and ketonemia.¹⁰ It frequently occurs as a consequence of absolute or relative insulin deficiency accompanied by an increased secretion of the counterregulatory hormones (cortisol, glucagon, epinephrine).¹¹ These hormone changes lead to a more marked hepatic gluconeogenesis and glycogenolysis, prompting severe hyperglycemia. Glycogen stores are depleted, and gluconeogenesis is enhanced, partly because of high levels of glucose precursors (and glycerol in particular), as a result of the increased lipolysis and of amino acids from muscle breakdown. Insulin resistance is responsible for the increased lipolysis, which in turn reduces the adipocytes' capacity to store free fatty acids, which are

metabolized as an alternative energy source in the process of ketogenesis.^{10,12} In particular, the excessive beta-oxidation of fatty acids prompts the formation of large quantities of acetyl CoA, which is then converted by the liver into ketone bodies (3-beta-hydroxy-butyrate and acetoacetate). Acetoacetate undergoes decarboxylation and conversion into acetone. The abundant ketone bodies, and particularly 3-beta-hydroxy-butyrate and lactic acid (which is also used in gluconeogenesis), are the main contributors to the metabolic acidosis.¹²

It is important to bear in mind that the metabolic changes characteristics of DKA trigger a chain of events that become self-perpetuating in a vicious cycle. Hyperglycemia gives rise to an osmotic gradient that results in an excessive diuresis, leading to severe dehydration and hypovolemia.¹⁰⁻¹² This further exacerbates the hyperglycemia and acidosis due to the activation of other counterregulatory hormones (cortisol growth hormone), and the osmotic diuresis causes low sodium levels. The shortage of insulin also leads to protein breakdown and interferes with cellular potassium uptake so that normal or high serum potassium levels can coincide with low total body potassium.¹⁰⁻¹²

Ketoacidosis and pregnancy

Pregnancy is characterized by insulin resistance, accelerated starvation, and respiratory alkalosis, especially in the second and third trimesters.¹³ It has been demonstrated that sensitivity to insulin decreases in pregnancy, reaching its nadir in the third trimester and rapidly returning to prepregnancy levels after delivery.¹³⁻¹⁵ Although the specific mechanisms behind the gradual onset of insulin resistance, often with a concomitant increase in insulin secretion, during pregnancy have not been fully clarified, an important contribution comes from the endocrine changes characteristic of pregnancy, including increased levels of estrogens, progesterone, human placental lactogen (HPL), cortisol, and TNF α .^{16,17}

The gradual decline in insulin sensitivity occurring in normal pregnancy was demonstrated in a clamp study by Catalano et al.,¹⁵ who found insulin sensitivity 56% lower in normal pregnant women during their third trimester. This is considered a physiological mechanism to facilitate the supply of glucose to the fetus, and it coincides with a parallel gradual

increase in insulin secretion to maintain a normal glucose tolerance.^{13,14} The gradient of the glucose concentration from mother to fetus is raised by means of higher postprandial glucose levels in pregnant women. During fasting, their insulin resistance promotes the release of fatty acids that the mother can use as an alternative fuel, thereby keeping the glucose for the fetus, and this explains the states of accelerated starvation and facilitated anabolism. High levels of human chorionic gonadotropin are also often associated with nausea and vomiting, which may give rise to a state of starvation, dehydration, and acidosis, with the subsequent activation of stress-related hormones.¹⁸ Then progesterone reduces gastrointestinal motility and increases carbohydrate absorption, thus raising plasma glucose levels. In pregnancy complicated by type 1 diabetes, the total absence of exogenous insulin hinders the achievement of an appropriate balance between the accelerated starvation and facilitated anabolism characteristic of pregnancy. This explains why it is difficult to keep glucose levels within the normal range, and, when hyperglycemia is not treated promptly, the pregnancy-induced lipolysis makes patients more susceptible to ketoacidosis. In pregnant women with type 2 diabetes, the pregnancy-related drop in insulin sensitivity overlaps the patient's preexisting insulin resistance, meaning that these patients need insulin therapy early in their pregnancy to avoid ketoacidosis. We need to bear in mind that maternal ketone body levels are elevated by 33% higher during the third trimester of pregnancy than in the postpartum period.^{12,19} Finally, a greater alveolar ventilation in pregnant women gives rise to a state of respiratory alkalosis that is overcome by means of an increased renal excretion of bicarbonate, which leads to a lower buffering capacity. These changes can trigger the onset of ketoacidosis at lower glycemic levels than those seen in diabetic women who are not pregnant²⁰ (Figure 56.1).

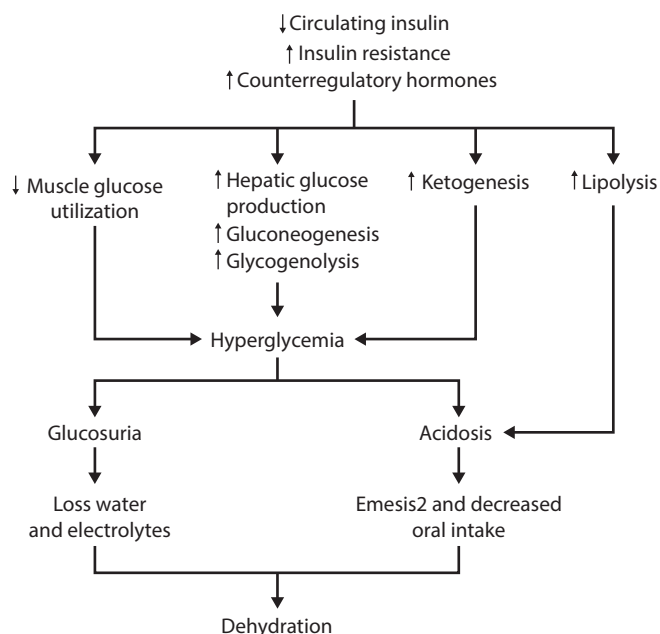


Figure 56.1 Pathophysiology of diabetic ketoacidosis in pregnancy.

Table 56.1 Factors triggering diabetic ketoacidosis

Starvation
Protracted vomiting
Infections
Insulin pump failure
Undiagnosed diabetes
Poor control of diabetes and/or poor compliance
Use of beta-sympathomimetic drugs for tocolysis
Use of steroid drugs for fetal lung maturation
Diabetic gastroparesis

Factors triggering DKA

The most common factors involved in the onset of DKA in pregnant women are listed in Table 56.1.

In a review conducted by Rodgers and Rodgers,²¹ the use of beta-sympathomimetic agents for tocolysis accounted for 57% of cases, while patient compliance issues and physicians' patient management errors were responsible for 24% and 16% of cases, respectively. The authors reported that diabetic gastroparesis, when associated with nausea, vomiting, and dehydration, contributes to triggering ketoacidosis. Infections and a history of missing doses of insulin therapy were the most important causes of ketoacidosis in a retrospective analysis conducted by Schneider, accounting, respectively, for 27% and 18% of cases.²² Other causes include insulin pump failure (in 13% of the cases reported by Chen²³), chronic corticosteroid therapy, undiagnosed diabetes, and smoking.^{24,25}

Euglycemic ketoacidosis

Euglycemic ketoacidosis is a severe form of ketoacidosis with serum bicarbonate levels of 10 mEq/L or less, in the absence of hyperglycemia (blood glucose levels below 10 mmol/L). First described by Munro et al. in 1973,²⁶ it has since been reported by several clinicians^{26–30} in women with both pregestational (type 1 and type 2) diabetes and GDM.^{26–30} True euglycemic ketoacidosis is rare, with only 0.8%–1.1% of all episodes meeting the aforementioned plasma bicarbonate concentration criterion.⁵ The fetal and placental demand for glucose (approximately 150 g/day), the increased renal excretion of glucose, the mother's higher glucose consumption, and the physiological hemodilution occurring in pregnancy all contribute to explaining why DKA can occur rapidly and at lower glucose levels in women who are pregnant than in those who are not.

Clinical presentation

The symptoms of diabetic DKA in pregnancy are no different from those seen in women who are not pregnant, except that they tend to develop more rapidly in pregnancy (Table 56.2). Patients usually present with a generalized malaise, nausea,

Table 56.2 Clinical presentation of diabetic ketoacidosis

Nausea/vomiting
Polydipsia
Polyuria
Weakness
Weight loss
Abdominal pain
Hyperventilation/fruity breath
Dry mucous membranes
Hypotension
Mental status changes
Coma

vomiting, polyuria, polydipsia, weakness, tachypnea, and signs of dehydration (flaccid skin, dry mucous membranes, tachycardia, hypotension, change in mental status). Abdominal pain due to a reduced peripheral perfusion may be severe and accompanied by uterine contractions. When infection is the precipitating factor, patients may have fever or, paradoxically, hypothermia in some cases (due to the vasodilatory effects of the hydrogen ions in excess when severe ketoacidosis develops).³¹ In the advanced stages of the disease, patients may have Kussmaul respiration, a breath with a classic fruity smell, lethargy, and signs of central nervous system involvement such as disorientation, obtundation, and coma due to cerebral edema.³²

Laboratory findings

The laboratory tests performed in cases of diabetic DKA are shown in Table 56.3. The analyses must include testing serum glucose levels, serum electrolytes, osmolarity, blood urea nitrogen, creatinine, arterial blood gas and serum bicarbonate levels, anion gap, and serum ketones, a complete blood cell count, liver function tests, and urine analysis. Hyperglycemia (plasma glucose levels higher than 300 mg/dL), an increased anion gap, an arterial pH lower than 7.3, ketosis (positivity for serum and urine ketosis), and decreased serum bicarbonate levels are characteristic of DKA. It is worth emphasizing, however, that plasma glucose levels may be lower in pregnancy than in diabetic women

Table 56.3 Laboratory findings in diabetic ketoacidosis

Hyperglycemia	>300 mg/dL 16.7 mmol/L
Arterial pH acidosis	<7.3
Serum HCO ₃	<15 mEq/L
Serum acetone	Positive
Anion gap	>12 mEq/L
Osmolality	>280 mOsm/kg

who are not pregnant (euglycemic ketoacidosis)^{18–23}; furthermore, ketoacidosis in diabetic pregnant women develops more rapidly than in nonpregnant women, and this can result in a delayed recognition and treatment.²⁷ The main ketones to be increased in ketoacidosis is beta-OHB, and neither acetone nor beta-OHB react as strongly as acetoacetate with nitroprusside (used to test for the presence of ketosis in urine), so the severity of a patient's hyperketonemia may be underestimated if only urine is tested, and that is why it is essential to test plasma ketone bodies too. After insulin infusion, beta-OHB is rapidly converted into acetoacetate so the ketone body levels in urine increase—even though the patient's ketoacidosis is regressing. Patients may have normal or high potassium levels, but it is important to consider that their total body potassium is generally low, and they become dehydrated and hypokalemic. Creatinine levels and blood urea nitrogen may be high as a result of renal dysfunction.¹⁰

Maternal and perinatal complications

DKA is fortunately uncommon in pregnancy, but it can result in such serious maternal complications as acute renal failure, respiratory distress syndrome, myocardial ischemia, cerebral edema, and death.^{7,8} The rate of occurrence of these complications depends on the mother's condition at the time of onset of DKA and on how the condition is managed. Recent data indicate a DKA-related maternal mortality rate of less than 1% and a fetal mortality rate of 9%–36%.^{6,22,24}

The rates of fetal complications such as fetal loss, preterm delivery, hypoxia, and acidosis are still high among the newborn of diabetic mothers with DKA.

Animal studies have shown that maternal ketoacidosis and hyperglycemia can lead to lactic acidosis and hypoxia in the fetus.^{33,34} This acidosis can occur via several pathways: fetal hyperglycemia results in fetal osmotic diuresis and hypovolemia, contributing to lactic acidosis; fetal hyperinsulinemia increases the fetal oxygen demand; and the mother's hemoglobin has a greater affinity for oxygen due to decreased 2,3-DPG levels, and this lowers the amount of oxygen available to the fetus.³⁵

High keto acid levels in pregnancy have been associated with a lower IQ score as well as a worse mental development score during the second year of life.³⁶ An association has also been reported between ketonuria measured during prenatal visits and adverse neurobehavioral outcomes even for non-diabetic pregnant women.³⁷

The fetal brain is particularly susceptible to higher than normal levels of β -hydroxybutyrate and lactate concentrations, which limit its glucose uptake.³⁸ These substances are known to accumulate in the basal ganglia of children during episodes of DKA.^{39,40} The acidotic environment that develops has been associated with a poor myelination and a weak cortical connectivity as well as with aberrations in hippocampal neurons—findings linked to expressive language impairments in children with autistic spectrum disorders.⁴¹

DKA management

DKA during pregnancy is an obstetric and medical emergency that warrants intensive treatment at a specialized care unit. The principles of DKA management in pregnancy are the same as for patients who are not pregnant. Treatment for DKA includes fluid replacement, insulin therapy, correcting acidosis and abnormal electrolytes, and treating the underlying disease, associated with intensive monitoring of maternal and fetal conditions (Table 56.4).

Fluid replacement

Patients with DKA may have a fluid deficit amounting to a mean 100 mL/kg of body weight⁴² and ranging from 6 to 10 L,⁴² with a total fluid loss of 100–150 mL/kg actual body weight.⁴³

Initial intravenous replacement solutions should consist of isotonic saline (0.9% NaCl) solution at 1000 mL/h for at least 2 hours. The use of hypotonic saline solution (0.45% NaCl) in the early phase of fluid replacement can raise the risk of cerebral edema.⁴⁴

After administering an initial 2 L of isotonic saline, in the presence of hypernatremia, the solution may be changed to a hypotonic saline (0.45% NaCl) delivered at 250 mL/h, a rate matching the electrolyte loss during osmotic diuresis, until serum glucose levels are between 200 and 250 mg/dL. Once glucose levels have dropped to lower than 250 mg/dL, the saline solution could be replaced with a 5% dextrose solution to prevent an excessively rapid drop of glucose levels.

Insulin therapy

Insulin treatment has to be initiated to correct the metabolic disorder. It is preferable to start with intravenous boluses and follow up with continuous intravenous infusions rather than to administer insulin via an intramuscular or subcutaneous route because a lower than normal tissue perfusion

can affect insulin absorption.⁸ Initial insulin boluses should contain approximately 10–15 U of regular insulin (0.1 U/kg), and the follow-on continuous insulin infusion could be at 0.1 U/kg/h, testing glucose levels hourly. If glucose levels drop too quickly, then there may be excessive displacements of water inside cells due to the rapid drop in serum osmolarity. Serum glucose levels should ideally drop by approximately 50–75 mg/dL/h. Continuous insulin infusions should be given until metabolic alterations have been corrected and patients are able to resume their regular diet and switch to their regular subcutaneous insulin treatment regimen.

Potassium

Potassium depletion may be substantial, and the correction of acidosis, the administration of insulin, and fluid replacements can shift the ion from the extracellular to the intracellular medium. In DKA, the total potassium deficiency is about 5–10 mEq/L. To prevent fatal arrhythmias, it is important to keep potassium levels between 4 and 5 mEq/L. Potassium levels should be monitored every 2–4 hours, and replacement potassium should be administered slowly (≤ 20 mEq/h) to avoid hyperkalemia and the risk of cardiac arrhythmia. Potassium replacement can be achieved either by adding KCl (40 mEq/L) to the replacement fluid administered, in an infusion administered at 140–250 mL/h, or by means of intermittent intravenous boluses of 10 mEq/h every 4–6 hours.⁴³

Acidosis correction

Correcting acidosis with intravenous bicarbonate is rarely recommended in the protocols for DKA management. The administration of bicarbonate may be associated with profound alkalosis or worsening acidosis secondary to an increase in the partial pressure of carbon dioxide, which can lead in turn to an impaired fetal oxygen transfer.⁸

For a pH <7.0 or serum bicarbonate levels <5 mEq/L, it is advisable to administer 50 mEq of bicarbonate.

Table 56.4 Treatment for diabetic ketoacidosis in pregnancy

1. Fluids
 - a. Isotonic saline solution
 - b. Total replacement in the first 12 hours with 4–6 L
 - i. 1 L in the first hour.
 - ii. 500–1000 mL/hour for 2–4 hours.
 - iii. 250 mL/hour up to 80% fluid replacement.
 - iv. In cases of hypernatremia, use 0.45% saline solution.
 - c. Glucose, starting with a 5% dextrose infusion, when glucose levels drop < 250 mg/dL (14 mmol/L)
2. Electrolytes
 - a. Potassium
 - i. If normal or low, begin with 15–20 mEq/hour.
 - ii. If high, wait until it drops to within normal range, then 20–30 mEq/L.
 - b. Bicarbonate: 44 mEq if pH < 7.0
3. Insulin
 - a. An initial bolus of 10–15 U of regular insulin (0.2–0.4 U/kg)
 - b. Intravenous infusion with 2–10 U/hour

Oxygenation

Maximizing tissue oxygenation in the mother and oxygen supply to the uterus and placenta are essential aspects of acute DKA management. Fetal hypoxia and fetal distress may occur during maternal acidemia. Oxygen administered through a face mask, hydration, and left lateral decubitus of the mother can help to maximize uteroplacental perfusion and fetal oxygenation.

Managing of precipitating factors

Among precipitating factors for the onset of DKA infections must be bear in mind. Possible sources of infection include the urinary tract, the upper airways, the gallbladder, the ear, a tooth abscess, cellulitis, and wound infections after surgery. It is mandatory to identify and treat these issues with appropriate antibiotics and/or surgery.

Fetal monitoring and timing of delivery

Maternal DKA results in fetal hypoxemia and acidosis. Fetal heart rate monitoring is recommended from 24 weeks of gestation onward. During episodes of DKA, fetal heart rate monitoring shows minimal variability, absent accelerations, and repetitive variable and late decelerations. Furthermore, the fetal biophysical profile may be abnormal and the blood flow redistributed. The frequency and severity of these abnormalities depends on the severity and duration of the DKA.⁴⁵

As concerns the timing of delivery, this will depend on the gestational age of the fetus, the condition of mother and child, and their response to treatment. It is essential to stabilize the mother's condition.

Prevention

Prepregnancy counseling for diabetic women should include providing information on their risk of DKA. Women with pregestational diabetes should be thoroughly informed of the importance of compliance with dietary restrictions, exercise, and therapy (especially their insulin dosage and its means of administration, e.g., pumps). All women have to be aware that if their glucose levels are higher than 200 mg/dL, it becomes necessary for them to test their blood or urine ketone body levels and to contact their physician if the test result is positive. Infections, nausea and vomiting, diarrhea, and polyuria are all conditions that carry a high risk of DKA and warrant hospitalization.

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57 Thyroid disease in pregnancy

Yoel Toledano and Gabriella Solomon

Pregnancy has a profound effect on the thyroid gland function. Numerous physiological changes occur during pregnancy including hormonal alterations and increased metabolic demands. Thyroid disorders may affect the progression of pregnancy, the pregnant woman, and the developing fetus. On the other hand, pregnancy may also affect the course and the treatment of thyroid disorders. Hence, diagnosis and treatment of thyroid disorders in pregnancy parallel that of nonpregnant women, but present unique problems.

Maternal thyroid physiology

Thyroid hormone production and secretion is regulated by pituitary thyroid-stimulating hormone (TSH), with a negative feedback loop, i.e., TSH production and secretion are suppressed when thyroid hormone levels are increased. For the vast majority of clinical situations, TSH is considered as the single best screening test for primary thyroid dysfunction. Thus, a low serum TSH level, in the presence of a high serum-free T₄ (FT₄) and/or free T₃ (FT₃) levels, is characteristic of primary hyperthyroidism. Alternatively, a high serum TSH level in the presence of a reduced serum FT₄ level is characteristic of primary hypothyroidism. The main changes in thyroid physiology during pregnancy include thyrotropin (TSH) receptor stimulation by human chorionic gonadotropin (hCG) and increased serum thyroxine binding globulin (TBG) concentrations and iodine requirements.

Human chorionic gonadotropin

As TSH and hCG are both glycoprotein hormones with considerable homology, the rising hCG level during early pregnancy, with peak at 10–12 weeks, probably has a weak thyroid stimulatory activity. Consequently, the elevated serum hCG concentration is accompanied by a reciprocal fall in TSH level. This effect is more pronounced at higher hCG levels as is seen in twin pregnancies.¹ Near the end of the first trimester (peak circulating hCG), there is a small and transient increase in FT₄ levels, usually within the normal range. Regarding physiological changes in pregnancy, transient gestational hyperthyroidism and/or hyperemesis gravidarum may reflect the extreme end of the spectrum.^{2,3}

Thyroxine binding globulin

During pregnancy, estrogen increases serum TBG concentration about twofold by elevated production and decreased clearance. To maintain adequate free thyroid hormone concentrations during this period, thyroid hormone production increases until a new equilibrium is reached and plateaus at approximately 16 weeks of gestation.¹

Iodine and pregnancy

Iodine requirements are higher in pregnancy due to enhanced T₄ production, increased renal iodine clearance, and fetal iodine demands. Maternal iodine deficiency can result in impaired maternal and fetal thyroid hormone synthesis. Severe iodine deficiency in a given population has been associated with decreased fertility, spontaneous abortion, increased perinatal and infant mortality, endemic goiter, and endemic mental retardation.⁴ Moreover, it can lead to endemic cretinism characterized by irreversible mental retardation, with either a neurological syndrome such as deaf-mutism and motor rigidity or predominant hypothyroidism or a combination.⁴

The prophylactic action of treatment with iodine on the incidence of cretinism demonstrates the fundamental etiological role of iodine deficiency. Iodine deficiency is the leading cause of preventable mental retardation worldwide.⁵ Prolonged enhanced thyroid stimulation by even mild to moderate iodine deficiency can lead to gradual decline in total body iodine stores and goiter formation.⁶ Iodine intake and methods to treat and avoid iodine deficiency differ between countries. The World Health Organization recommends 250 µg of iodine daily during pregnancy and lactation and 150 µg/day for women of reproductive age.⁷ Accordingly, the American Thyroid Association (ATA) has recommended a 150 µg daily iodine supplementation for pregnant and breastfeeding women in North America in order to achieve the total of 250 µg iodine ingestion per day.⁸

Thyroid function in the fetus

At 10th–12th week of gestation, fetal TSH appears in the pituitary gland. At the same time, the thyroid gland is capable of concentrating iodine and synthesizing thyroid hormones. Hormone synthesis is little until midgestation. Thereafter, fetal thyroid production and secretion increase

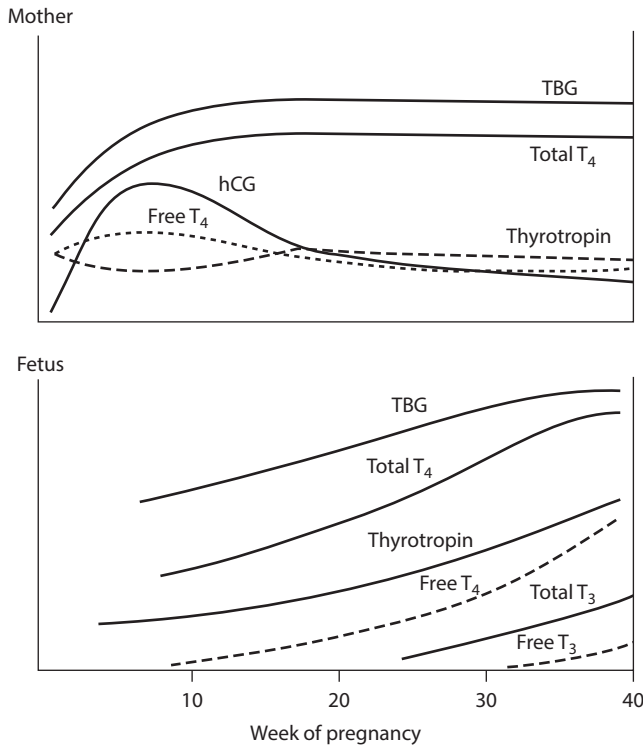


Figure 57.1 Relative changes in maternal and fetal thyroid function during pregnancy. hCG, human chorionic gonadotropin; TBG, thyroxine binding globulin. (Adapted from Burrow, G.N. et al., *N. Engl. J. Med.*, 331(16), 1072, 1994. With permission.)

gradually⁹ (Figure 57.1). Thyroid hormones have a major role in the normal growth and development of the brain and central nervous system.^{10–12}

During early pregnancy, maternal thyroid hormones can be an important source necessary for early fetal

neurodevelopment. Concordantly, there is evidence that maternal thyroid hormones partially cross the placenta.¹³

Assessment of thyroid function in pregnancy

The following thyroid function tests are affected by the altered thyroid physiology in pregnancy.

Thyroid-stimulating hormone

There is mounting evidence that the reference range for serum TSH levels is lower in pregnancy compared with the nonpregnant state. The largest TSH level decrease is observed during the first trimester (Figure 57.2). Recently, the upper normal limit during the first trimester has been accepted as 2.5 mIU/L, as recommended in the guidelines of several professional societies (Table 57.1).

Thyroid hormones

Serum FT4 level is usually within the normal range. However, measuring FT4 by commonly used immunoassay methods may be unreliable due to alterations in serum proteins during pregnancy. Hence, awareness is needed. It is recommended to use method-specific and trimester-specific laboratory range if available.¹⁸ As expected, total T4 concentration reference range is approximately 1.5 times the nonpregnant level by 16 weeks of gestation.¹⁹

Hypothyroidism

Although maternal hypothyroidism is associated with menstrual disturbance and decreased fertility, it is not rare to conceive.²⁰ Women with limited thyroid reserve or iodine deficiency can develop hypothyroidism due to the increased metabolic demands during pregnancy. When iodine intake

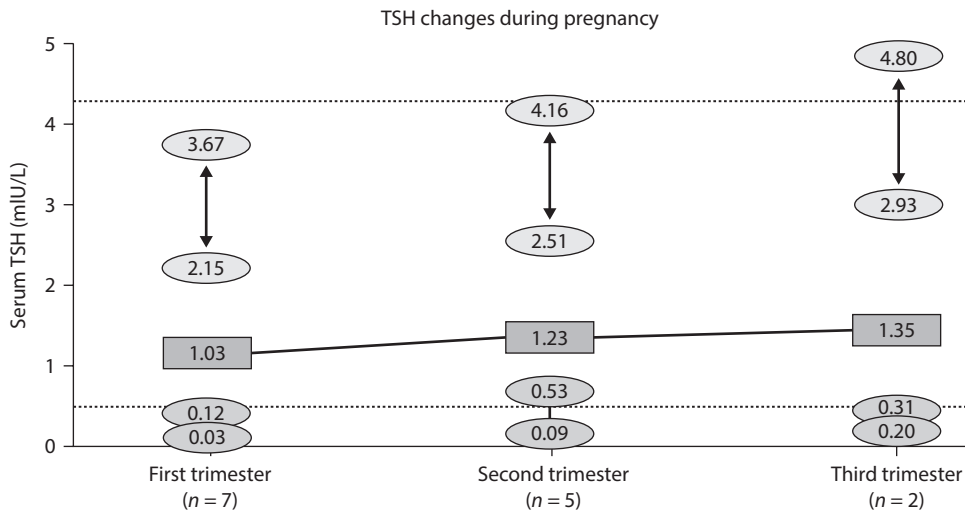


Figure 57.2 TSH changes during pregnancy—trimester-specific TSH reference intervals. Median values (rectangle) versus the range of 2.5th (ellipse, bottom) and 97.5th (ellipse, top) percentiles for each trimester of pregnancy taken from eight studies of trimester-specific TSH reference intervals, reported between 2004 and 2009, for women without thyroid peroxidase autoantibodies from iodine-sufficient populations. The dotted horizontal lines show the typical nonpregnant reference range (0.4–4.1 mIU/mL). (Adapted from Glinioer, D. and Spencer, C.A., *Nat. Rev. Endocrinol.*, 6(9), 527, 2010. With permission.)

Table 57.1 Thyroid-stimulating hormone trimester-specific reference ranges: Recommendations in recent clinical guidelines

Trimester-specific reference range for TSH (mIU/L)			
	ATA 2011 ¹⁵	AACE and ATA 2012 ¹⁶	Endocrine Society 2012 ¹⁷
First trimester	0.1–2.5	Upper normal < 2.5	0.1–2.5
Second trimester	0.2–3.0	Upper normal < 3.0	0.1–2.5
Third trimester	0.3–3.0	Upper normal < 3.5	

Note: These cutoff values are recommended in case the local laboratory does not provide trimester specific reference ranges.

Abbreviations: ATA, American Thyroid Association; AACE, American Association of Clinical Endocrinologists.

is adequate, the most common cause of hypothyroidism during pregnancy is autoimmune thyroid disease (AITD) (Hashimoto's thyroiditis).²¹ Also, the presence of other autoimmune disorders like type 1 diabetes mellitus raises the risk of AITD.²² In iodine-poor areas, iodine deficiency itself is the most frequent cause of hypothyroidism. In fact, iodine deprivation is the most common cause of hypothyroidism worldwide. Next, other etiologies can occur in pregnant women including prior radioiodine ablation of the thyroid, thyroidectomy, or secondary hypothyroidism e.g., Sheehan's syndrome. Finally, an important cause for neonatal thyroid hypofunction is congenital hypothyroidism. Most cases of this disorder are due to agenesis or dysgenesis of the fetal thyroid gland, congenital dysmorphogenesis, or iodine deficiency in endemic areas.

Symptoms and signs of hypothyroidism during pregnancy are the same as in the nonpregnant state. They include sensitivity to cold, dry skin, constipation, fatigue, muscle cramps, weight gain, voice change, and drowsiness. The symptoms may be nonspecific or may go unnoticed. Notably, many patients are asymptomatic. Regarding congenital hypothyroidism, it is a very common cause of intellectual disability that can be prevented. Thyroid function tests confirm the diagnosis of hypothyroidism. An elevated serum TSH level, in combination with a subnormal serum FT4 level, characterizes overt/primary hypothyroidism. Furthermore, serum TSH level elevation above 10 mIU/L, irrespective of serum FT4 levels, is also considered as overt hypothyroidism by the ATA.¹⁵

Next, subclinical hypothyroidism (SCH) is characterized by a serum TSH above the upper reference limit (using pregnancy-specific reference ranges) in combination with a normal serum FT4 concentration. However, in secondary and tertiary (central) hypothyroidism, the diagnosis should be based on a low serum FT4 and low-normal serum TSH levels.

An additional thyroid function disorder during gestation is isolated hypothyroxinemia (low T4). It is defined as a maternal FT4 concentration in the lower 5th or 10th percentile of the reference range, in conjunction with a normal TSH. The effect of isolated maternal hypothyroxinemia on perinatal and neonatal outcome is yet unclear. Indeed, in mothers with isolated hypothyroxinemia treated or not with T4 before 20 weeks gestation, the IQ of children was not affected.²³

Overall, the prevalence of overt and SCH in pregnancy is estimated to be 0.3%–0.5% and 2%–2.5%, respectively. The prevalence may be higher in iodine insufficient areas.^{24,25} Screening programs detect congenital hypothyroidism in approximately 1:2000 to 1:4000 newborns.²⁶

Maternal and fetal complications of hypothyroidism

Hypothyroidism during pregnancy may adversely affect maternal and fetal outcomes. It has been associated with an increased risk of spontaneous abortion. In continuing pregnancies, hypothyroidism has been associated with increased risk of several complications such as preterm delivery, gestational hypertension, placental abruption, low birth weight, cesarean section, and postpartum hemorrhage.^{4,20,27–29} Conversely, no difference in adverse pregnancy outcomes was detected in a study of women with antenatal severe hypothyroidism, defined as TSH level above 20.0 mIU/L, compared to a control euthyroid group. Hirsch et al. concluded that intense follow-up and levothyroxine replacement therapy during gestation may improve pregnancy outcomes, even when target serum TSH levels are not reached.³⁰

Women with SCH were also at increased risk for adverse pregnancy outcomes in some (but not all) studies, though lower than overt hypothyroidism. The complications included spontaneous abortion, preterm delivery, placental abruption, and pregnancy loss.^{20,25,31,32} The adverse outcomes have varied between studies.

Importantly, maternal hypothyroidism has been associated with impairment in psychomotor development in the offspring.^{12,32,33} The full IQ scores of children at age 7–9 years, born to hypothyroid women (mean TSH 13.2 mIU/L), were four points lower in average compared with euthyroid controls. Strikingly, the test scores of children of untreated hypothyroid women were seven points lower than controls, but the test scores of children whose mothers were treated (although inadequately) were similar in most categories to the control children.³³ Correspondingly, the association of cognitive development and SCH in pregnancy is still under study. Recently, a randomized study was reported on the cognitive examination of children whose mothers received levothyroxine therapy during pregnancy for impaired thyroid function tests (mean maternal serum TSH was 3.8 mIU/L).

No benefit in cognitive function, assessed at age 3 years, was detected versus controls.³⁴ More randomized trials are needed to determine the benefit of SCH treatment on neurocognitive outcomes in early pregnancy.

Treatment of hypothyroidism

It is well accepted that maternal hypothyroidism should be treated considering the risks to both the mother and the fetus. The recommended treatment for hypothyroidism is oral synthetic L-T4 (levothyroxine or L-thyroxine). The goal of L-T4 replacement during gestation is to restore euthyroidism as soon as possible. Treatment with L-T4 is usually initiated with a dose of 100–150 µg/day or close to full replacement doses (1.6 mcg/kg body weight/day), but individual dose requirements vary widely. Milder hypothyroidism may require a lower dose. The normal trimester reference ranges for TSH are used as target of treatment during pregnancy.^{15–17}

In most of the pregnant women already treated with L-T4, early dose adjustment is needed as soon as pregnancy is confirmed in order to meet the increased requirement during pregnancy. Requirements increase as early as the fifth week of gestation.³⁵ Optimizing preconception TSH level (<2.5 mIU/L) is recommended for hypothyroid women anticipating pregnancy.¹⁵ There is an indication that lower TSH levels before pregnancy (to the lower quartile of normal) might reduce the risk of elevated levels in pregnancy.³⁶ Adjustment may require 30% increase in dosage or more.³⁷

Strategy for increasing L-T4 dose should be individualized. Factors like preconception TSH level and etiology of maternal hypothyroidism may provide insight into the magnitude of the needed increase. Dose increase is more likely to be required in patients without a functional thyroid tissue (e.g., due to radio-ablation or surgery) than in patients with Hashimoto's thyroiditis.³⁸

Next, treatment of hypothyroidism should be monitored. L-T4 has a long half-life of almost seven days. Hence, a peak therapeutic effect at a given dose may not be attained for 4–6 weeks. Correspondingly, monitoring TSH levels every 4–6 weeks is recommended during the first half of pregnancy. Actually, monitoring every 4 weeks can detect 92% of abnormal values.³⁷ In the second half of pregnancy, it is reasonable to monitor TSH levels at least once between 26–32 weeks gestation and also 4–6 weeks after changing dosage or brand, as new equilibrium is expected.³⁷ After delivery, most hypothyroid women need to decrease the L-T4 dosage administered during pregnancy to the prepregnancy dose.

Regarding treatment of SCH during pregnancy, there is no consensus.^{39,40} Reduction in adverse pregnancy outcomes was demonstrated in a study of women with SCH and positive TPO-Ab treated with L-T4.³⁹ Recently, several professional societies addressed this issue but had controversial opinions. For example, the ATA recommended L-T4 treatment in pregnant women with SCH who are also thyroid peroxidase antibody positive (TPO-Ab+).¹⁵ Instead, the Endocrine Society recommended replacement in all pregnant women with SCH.¹⁷ From our perspective (Toledano and Solomon, the authors of this chapter), we also recommend offering

treatment for all pregnant women with SCH as we expect that the benefits outweigh any potential risks. However, close monitoring of thyroid function is highly recommended in case the therapeutic decision was not to treat.

Finally, assessment of treatment in secondary and tertiary (central) hypothyroidism should be guided by FT4 and not TSH.

Screening for hypothyroidism

Universal screening for hypothyroidism in asymptomatic women who are pregnant or are planning pregnancy is controversial due to insufficient evidence that it is beneficial.³⁹ Indeed, screening practices and guidelines vary widely. Some professional societies updated these clinical practice guidelines and recommended “targeted” or “aggressive case finding” rather than universal screening.^{15,17}

Concordantly, the ATA recommends thyroid function testing in women at high risk for overt hypothyroidism¹⁵:

History of thyroid dysfunction or prior thyroid surgery
 Age > 30 years
 Symptoms of thyroid dysfunction or the presence of goiter
 TPO-Ab positivity
 Type 1 diabetes or other autoimmune disorders
 History of miscarriage or preterm delivery
 History of head or neck radiation
 Family history of thyroid dysfunction
 Morbid obesity (BMI > 40 kg/m²)
 Use of amiodarone or lithium or recent administration of iodinated radiological contrast
 Infertility
 Residing in an area of known moderate to severe iodine insufficiency

The time for screening is in early pregnancy. Indeed, the Endocrine Society recommends TSH screening either on the ninth week of gestation or on the first prenatal visit.¹⁷

Hyperthyroidism in pregnancy

Etiology

The prevalence of hyperthyroidism during pregnancy is relatively uncommon. It ranges between 0.1% and 1%. Approximately 0.4% and 0.6% of pregnant women present with clinical and subclinical hyperthyroidism, respectively.⁴¹ Etiologies of thyrotoxicosis include those that present specifically during pregnancy, as well as others found in the general population.

The most common etiology of hyperthyroidism in the childbearing age is Graves' disease (GD). This cause accounts for 85% of clinical hyperthyroidism in pregnancy. Also, another common etiology of thyrotoxicosis is hyperemesis gravidarum.⁴² In contrast, uncommon etiologies during pregnancy include silent or subacute thyroiditis, toxic

multinodular goiter, single toxic adenoma, molar disease, and struma ovarii.⁴³

Clinical diagnosis

The clinical characteristics are the same in pregnant and nonpregnant patients. However, the clinical diagnosis of hyperthyroidism during pregnancy may be challenging. Many nonspecific symptoms can be mimicked by normal pregnancy, e.g., anxiety, fatigue, heat intolerance, tachycardia, tremor, warm moist skin, and systolic murmur. Instead, several physical findings such as goiter, ophthalmopathy, and pretibial myxoedema are highly suggestive of GD. Another suspicious symptom of hyperthyroidism during gestation is weight loss or the absence of weight gain despite an increased appetite. When hyperemesis gravidarum is associated with weight loss, the differential diagnosis should include hCG-induced hyperthyroidism.

Laboratory diagnosis

Measurements of serum TSH, T4 and T3 levels, and anti-TSH receptor antibodies (TRAbs) are required when suspecting hyperthyroidism. Patients with prominent symptoms almost always have a suppressed serum TSH level <0.1 mU/L concurrently with elevated serum free T4 and T3 levels. Importantly, the evaluation of thyroid function tests must consider the hCG-mediated suppression of serum TSH that occurs during pregnancy. Furthermore, thyroid antibodies (thyroglobulin [Tg]-Ab and TPO-Ab) are usually positive in patients with GD. Hence, the differential diagnosis must include AITD as the etiology of hyperthyroidism. Not surprisingly, TRAbs are detectable in the majority of patients with GD. During the second half of pregnancy, TRAb production tends to undergo immunological remission. Thus, measurement of these antibodies is dependent on gestational age at determination.^{44,45}

Pregestational counseling for women with Graves' disease

Conceivably, pregestational counseling is extremely important in the treatment plan of young women with GD. Contraception counseling is strongly recommended in all women of childbearing age affected with GD. The main aim is to avoid pregnancy while having hyperthyroidism.^{41,42} The different therapeutic choices should be presented and discussed with women planning a pregnancy: medical treatment, radioiodine therapy, or surgery. A full discussion on the different choices can be found in reference 46.

Fetal and neonatal adverse effects

Fetal hyperthyroidism is a serious and rare complication. However, this potentially fatal disorder is preventable. Several risk factors were identified including active maternal Graves' hyperthyroidism (GH) and a history of GD treated with ablation therapy. It is recommended to determine the

TRAb titer between gestational weeks 22 and 26. When the titer is three to five times above normal, the fetus should be evaluated for detection of potential fetal hyperthyroidism. This condition can be assessed by several fetal ultrasonographic parameters: tachycardia (persistent fetal heart rate of >160 bpm), the presence of fetal goiter, increased fetal motility, growth retardation, and accelerated bone maturation.⁴³ A pattern of the fetal heart monitor tracing unique to fetal thyrotoxicosis⁴⁷ includes a sustained baseline of 170–180 beats/minute combined with moderate variability. The latter exhibits acceleration with a lack of deceleration. If the information to be gained will change therapy, it is possible to perform serial cordocentesis for diagnosis and monitoring drug therapy.^{48,49} Suspected fetal hyperthyroidism in utero can be treated with a combination of mercaptizol (MMI, 20 mg/day) and thyroxine, which is occasionally required to maintain maternal euthyroidism. Fortunately, neonatal GD with hyperthyroidism is presented in only 1%–5% of neonates born to mothers with GD. As discussed previously, the etiology is related to the transplacental passage of stimulating maternal TRAb. In fact, it is recommended to perform cord serum-free T4 and TSH determinations in all deliveries of mothers with a history of GD.

Fetal hypothyroidism: Maternal GD treated with anti-thyroid drugs (ATDs) may induce fetal hypothyroidism. Conceivably, keeping maternal circulating thyroid hormone levels in the upper quartile of the normal range is the best way to avoid fetal hypothyroidism.^{41,43} Inhibitory TRAb production has been shown to cause hypothyroidism transiently in neonates born to mothers with GD.^{50,51}

Management of Graves' disease in pregnancy

As a general rule, gradual improvement of GD occurs during gestation. Several causes were alluded to this spontaneous improvement including immunosuppressive effect of the pregnancy, elevation of maternal serum TBG levels that reduce serum-free T4 and T3 fractions, and iodine losses characteristic to the gestation period.

The key management for GD during pregnancy are the ATDs.^{41,43} In general, the two main targets of therapy are (1) controlling hyperthyroidism in the mother by maintaining free thyroid hormone levels at the upper limit of normal range or borderline high levels and (2) using the smallest possible dose of ATD in order to minimize the risk of fetal hyperthyroidism or hypothyroidism. Beneficial response to therapy includes weight gain and improvement in symptoms. Several adverse effects of ATD have been documented. First, propylthiouracil (PTU) is associated with risk of hepatic toxicity necessitating liver transplantation in a number of cases and may be fatal.^{52,53} Second, methimazole (MMI) treatment is infrequently associated with aplasia cutis in neonates. This is a localized lesion in the parietal area of the scalp. It is characterized by congenital absence of the skin and a punch-out, "ulcer" lesion.⁵⁴ Third, choanal atresia and/or esophageal atresia, minor dysmorphic features, and developmental delay are characteristic to the "methimazole embryopathy." Taken together, the FDA and

the ATA recommended to use PTU only in the first trimester of pregnancy. By the second trimester, PTU should be switched to MMI.⁵⁵

Simultaneously, symptoms of acute hyperthyroid disease may be controlled transiently by propranolol.

The second treatment option in pregnancy is surgery. Subtotal thyroidectomy is the preferred surgery and typically is performed in the second trimester. Indications to the surgical alternative are few: consumption of large ATD doses, allergy to ATD,⁵⁶ and patient preference.

As far as breastfeeding in mothers treated with ATD for GD is concerned, the risk to the neonates is insignificant. However, this hazard is low as long as the doses of ATD can be kept moderate (MMI <20 mg/dL; PTU <250–300 mg/dL).⁴³

Gestational transient thyrotoxicosis

Gestational transient thyrotoxicosis (GTT) or nonauto-immune gestational hyperthyroidism is a transient syndrome of hyperthyroidism occurring near the end of the first trimester of pregnancy, usually in healthy women. It is frequently related to excessive vomiting.⁴³ As its nature is transient, GTT may be clinically inapparent. The clinical and biochemical characteristics of thyrotoxicosis are usually mild and variable. They include mild thyroid enlargement and lack of thyroid autoantibodies.

The etiology of GTT was discussed earlier. Its prevalence is highly variable and ranges between 0.3% in Japan and 11% in Hong Kong.^{58,59} It may reach 2%–3% of unselected pregnancies in Europe, i.e., tenfold more prevalent than GD.⁵⁷ Since GTT improves in parallel to the decline in hCG levels, this syndrome is always transient. As a rule, partial or total suppression of serum TSH can last several weeks after serum free T4 reverts to normal.^{60,61} GTT usually has no adverse pregnancy outcome.

However, the most severe cases are commonly associated with hyperemesis gravidarum, e.g., twin pregnancy. Usually, no specific treatment is necessary. In some cases, administration of beta-adrenergic blocking agents, hydration, and antiemetics are required for a short period to relieve symptoms. Importantly, GD should be excluded in patients with a severe clinical presentation and clear symptomatic hyperthyroidism by measurement of TRAb. Transient PTU administration for a few weeks should be considered.

Nodular and malignant thyroid disease

The prevalence of nodular thyroid disease is not so rare. Up to 10% of pregnant women have thyroid nodules. Nodular thyroid disease was not associated with pregnancy in an iodine-deficient area.⁶² Furthermore, the incidence of thyroid cancer was reported in a retrospective study from the California Cancer Registry during the years 1991–1999: 3.3/100,000, 0.3/100,000, and 10.8/100,000 were diagnosed before pregnancy, at the time of delivery and within 1 year after delivery, respectively.⁶³

Diagnostic evaluation and management of a thyroid nodule in pregnancy

The first investigation of choice is fine-needle aspiration biopsy (FNAB). It can detect a malignancy/suspicious result in 35%.⁶⁴ Several management guidelines suggested the following approach for a single thyroid nodule detected on physical examination or for a dominant nodule in a multinodular gland, confirmed by ultrasonography:

1. Solid lesion <1 cm, follow-up in the postpartum.
2. Nodule >1–1.5 cm, should be considered for FNAB if there are suspicious findings on ultrasound.
3. In the presence of tracheal obstruction, immediate surgery.
4. If the FNAB is diagnostic of malignancy or it is a suspicious lesion, surgery may be postponed until after delivery, unless there is one of the following signs: presence of lymph node metastases, the lesion is a large primary or extensive lymph node involvement related to a medullary cancer.
5. Surgery and FNAB could both be postponed until after delivery with probable safety.
6. A woman with a malignant lesion or rapid growth should be offered surgery in the second trimester of gestation.
7. Some authors recommend that women with follicular lesions or early-stage papillary carcinoma may postpone the surgery until postpartum since these lesions are not expected to progress rapidly.^{15,65,66}

Pregnancy and coexisting thyroid malignancy

Currently, evidence suggests that treated differentiated thyroid cancer without the evidence of residual disease should not hamper planning pregnancy. Accordingly, Hirsch et al.⁶⁷ reported on 63 consecutive women (90 births), followed between 1992 and 2009 for papillary thyroid cancer. All women had delivered at least once after total thyroidectomy, and I-131 was also administered in 58 of them. A comparison of neck ultrasound and serum thyroglobulin (Tg) levels was performed before and after pregnancy. The conclusion was that gestation does not cause thyroid cancer recurrence in PTC survivors who have no structural or biochemical evidence of disease persistence at the time of conception. Hence, pregnancy has a minimal effect on thyroid cancer. Instead, it is possible that residual cancer at the time of conception will progress. More evidence is needed before making a firm recommendation.

As far as thyroid hormone administration is concerned, suppression and maintenance of serum TSH levels between 0.1 and 0.5 mU/L is prudent. Specifically, it is important in patients with a high-risk tumor recurrence but with no clinical or biochemical evidence of current disease. In analogy with this, TSH suppression is recommended in pregnant women with a positive or suspicious FNAB for cancer that prefer delaying surgery until postpartum. However, the level of serum TSH in this case should be detectable, i.e., suppressed only mildly. Next, adverse events with previous

I-131 therapy were not reported in subsequent pregnancies.⁶⁸ Following I-131 ablation therapy, it is strongly recommended to delay pregnancy for at least 1 year.

Postpartum thyroid dysfunction

Prominent changes in the immune system are detected during pregnancy.⁶⁹ Hence, the change in immune cellular status consists of an alteration from the Th1 to the Th2 state. Also, the humoral immune system alters. Generally, 10% of pregnant women have positive anti-TPO-Ab titer at 14–16 weeks gestation. However, it decreases considerably during the second and third trimesters. After delivery, the Th2 position reverts abruptly back to the nonpregnant Th1 state. Notably, this immune rebound phenomenon consists of a very pronounced elevation in the anti-TPO-Ab titer. Indeed, it reaches a peak between 3 and 6 months postpartum. Similarly, TRAb titer present in early pregnancy has the same pattern through gestation and postpartum. The postpartum immunological alterations discussed earlier can lead to the development of postpartum thyroid dysfunction (PPTD), and they may be either transient or permanent. Moreover, the dysfunction may be related to either a destructive or stimulating pathological process (Figure 57.3).

Postpartum Graves' disease

Significantly, women with GD in remission after ATD therapy have an increased risk for relapsing hyperthyroidism postpartum.⁷⁰ The differential diagnosis of postpartum hyperthyroidism requires clinical examination, measurement of circulating TRAb, thyroid scintiscanning, and radioiodine uptake.

Postpartum thyroiditis

It is estimated that 5%–9% of women have postpartum thyroiditis (PPT). Risk factors for this disease include a prior episode of PPT and type 1 diabetes. In fact, PPT is three-fold more prevalent in women with this diabetes versus

nondiabetics. As expected, PPT is strongly correlated to thyroid antibodies in women with type 1 diabetes. As discussed, 10% of pregnant women have positive antithyroid antibodies at 14–16 gestational weeks. PPTD occur in 50% of these women during the first 6 months after delivery.⁷¹ Of note, up to 50% of these patients may develop permanent hypothyroidism at 7–10 years postpartum.

The etiology of PPT is a destructive thyroiditis. It may present up to 9 months after delivery with a transient hyperthyroidism and/or hypothyroidism.⁷² Using the correlated thyroid function tests, it is possible to diagnose the specific thyroid dysfunction, i.e., hyperthyroidism or hypothyroidism. The clinical course include hyperthyroidism alone, hypothyroid phase alone, and hyperthyroidism followed by hypothyroidism in 19%, 49%, and 32% of patients, respectively. Remarkably, prominent symptoms in the hyperthyroid phase, and even in antibody-positive patients without any thyroid dysfunction, are irritability and lack of energy. Conversely, the hypothyroid status may present with intense symptomatology.

The diagnosis of PPT may be established by radioiodine uptake. After isotope administration, the uptake will be very low both at early and late times, consistent with the destructive nature of this disorder. Although antithyroid antibodies are frequently positive, TRAbs are negative.

Regarding the management of PPT, no specific therapy is generally required in the hyperthyroid phase as it is relatively asymptomatic. Beta-adrenoreceptor blocking agents may be administered for hyperthyroid symptoms and signs, e.g., palpitations, anxiety, sweating, or tachycardia. However, symptomatic and persistent hypothyroidism should be treated with L-thyroxine. As 50% of women with transient thyroid dysfunction postpartum will develop permanent hypothyroidism after 7–10 years, annual thyroid function test should be performed.

Thyroid autoimmunity

Infertility

Immunological factors may have adverse impact on normal fertility and reproduction processes including fertilization,

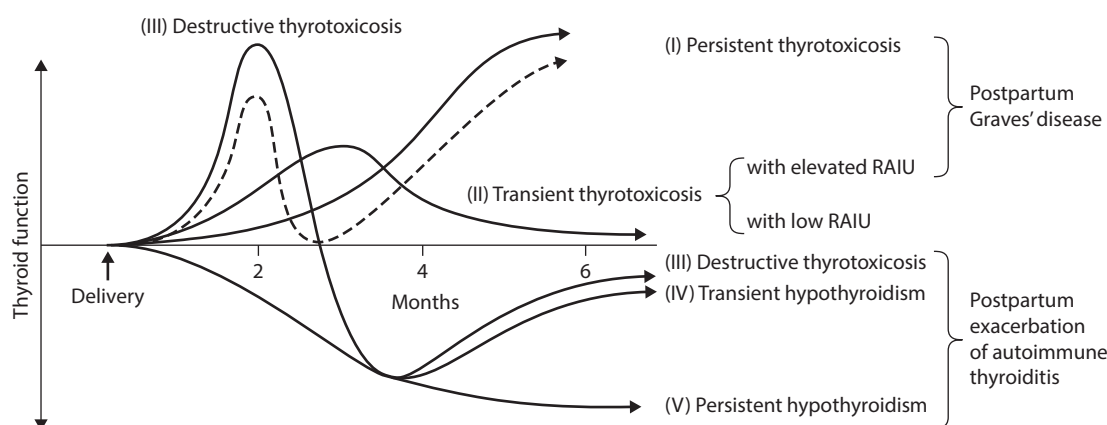


Figure 57.3 Patterns of postpartum thyroid dysfunction. (Adapted from Lazarus, J.H., *Eur. Thyroid J.*, 1, 24, 2012. With permission.)

implantation, and early embryo development. Indeed, the correlation between abnormal immunological laboratory tests, including antithyroid antibodies, and infertility is well established.^{73,74}

Regarding thyroid dysfunction, AITD, called also chronic lymphocytic thyroiditis or Hashimoto's disease, is the most common cause of hypothyroidism in women of reproductive age. Simultaneously, female infertility is correlated to clinical hypothyroidism. Medically assisted conception and onset of gestation is not hampered by AITD, but a successful outcome of the ongoing pregnancies is significantly reduced in those women with AITD due to greater early pregnancy loss.⁷⁵

Miscarriage

Several studies suggest that thyroid-antibody-positive women have a higher propensity to pregnancy loss, placental abruption, and even preterm delivery and become pregnant at an older age (approximately, 3–4 years older).^{76–84}

When thyroid hormone levels are compatible with euthyroidism, it is possible that in women with AITD these levels are actually inappropriately low for the given gestational period. Indeed, some reports suggested that L-thyroxine treatment may correct such minor deficiency. Moreover, this treatment may influence the systemic immune disorder and the placental–decidual environment.^{85–88} Of note, the association between thyroid autoimmunity and miscarriage still does not imply causation.^{89,90}

IVF

Currently, screening women with infertility and/or miscarriage for the presence of thyroid autoimmunity and dysfunction is routinely performed in many centers. However, several reports on women achieving a pregnancy through an IVF procedure have shown no correlation between the presence of thyroid autoimmunity and a risk for spontaneous miscarriage.^{75,91–96}

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58 Quality of care for the woman with diabetes at pregnancy

Alberto de Leiva, Rosa Corcoy, Alejandra de Leiva-Pérez, and Eulàlia Brugués

Quality assessment and improvement in diabetes care

The aim of healthcare is to achieve the best health outcomes in the most efficient manner, and the challenge for today's health delivery systems is to increase productivity and quality of care without increasing the economic costs.

Assessment of the quality of healthcare needs complex measures of the structure (staff, equipment, organization), the process (technical quality), and the outcomes (effectiveness, satisfaction, functional status, quality of life).

Healthcare delivery depends on efficient communication and cooperation among patients, healthcare services, and professionals; this matter is particularly critical with regard to chronic disorders in which effective shared care is pursued by multiple healthcare providers and professionals, enabling the patient to become actively involved in the process of their care. The effective share of related information is highly facilitated by the operation of an electronic patient record and a telematics infrastructure.

Healthcare delivery is moving toward disease management, focused on a patient-oriented approach, illness prevention promoting good health, and managing long-term care, all of which require integrated activities from generalists, specialists, and other healthcare professionals. This type of care requires effective coordination and an interrelated, multidisciplinary approach.

In addition, the implementation of effective strategies for continuous quality improvement takes advantage of four main areas: (1) efficient use of healthcare resources (e.g., eliminating practices that are clearly harmful, or without known benefits); (2) linking clinical research to clinical practice (evidence-based care); (3) application of new concepts for improvement of care (the process of care must comply with the "best practice," including solid methods to monitor and assess the outcomes); and (4) changing clinical practice (design of appropriate models for the management of healthcare services, based on valid, scientific information).

At a meeting held in St. Vincent, Italy, in October 1989, representatives of government health departments and patients' organizations from all European countries met diabetes experts to discuss a set of recommendations—the St. Vincent Declaration,¹ a joint initiative of the World Health Organization–Europe and the International Diabetes Federation–Europe (WHO/IDF)—with the intention of creating conditions allowing major reductions in deaths and the burden caused by diabetes mellitus. The declaration meant an important step forward in the general improvement in the quality of delivery of diabetes healthcare.

One of the main targets of the declaration was to establish monitoring and control systems using state-of-the-art information technology (IT) for quality assurance of diabetes healthcare provision. A European group of experts was established to design and implement mechanisms for the continuous improvement of the quality of diabetes care in Europe. The term continuous quality improvement was accepted to emphasize the progressive nature of the never-ending process after reaching a determined standard. The assessment requires the comparison of care with standards that are derived from scientific evidence, consensus, good practice, and clinical experience.

The St. Vincent Declaration pointed out that self-monitoring results in very effective control of treatment. Later in this chapter, the quality assessment of the procedures for self-monitoring glycemic control will be reviewed in some detail.

European DiabCare quality network

A subgroup of the St. Vincent Declaration Steering Committee was established to develop instruments and mechanisms for quality assurance in diabetes care. The first initiative of the DiabCare program was the development of the St. Vincent Diabetes Dataset from three main sources: (1) EuroDiabeta², a research project on modeling healthcare and the implementation of IT in diabetes; (2) the specific recommendations provided by the different working groups of the St. Vincent Declaration Steering Committee; and (3) the

advice provided by more than 130 expert diabetologists from 21³ European countries.

DiabCare Basic Information Sheet (BIS) contains 141 fields that include all the necessary data for the analysis of the quality of diabetes care (Figure 58.1). The pertinent analysis provides the performance of care in both aspects of process and outcomes (intermediate and final). Demographic data (age, sex, etc.) are required for a number of purposes. True patient outcomes include the burden of the medical end points of the St. Vincent Declaration (such as amputation, blindness). Symptoms of diabetes-related problems (e.g., painful neuropathy, angina pectoris) are also recorded. Specific outcomes regarding pregnancies are also included. For the measurement of quality of life, the DiabCare data sets only include information related to the duration of hospital admissions and the number of days without the ability to perform normal activities. Assessment of diabetic complications (retinopathy, nephropathy, neuropathy), cardiovascular risk factors, pharmacological treatment, and metabolic outcomes (glycated hemoglobin [HbA1c], lipid profile) was considered essential.⁴ The computer database (Figure 58.2) contains all the data items of the BIS and additional information with easy access by a single key stroke.

Once a year, at least, the data of all patients under care must be collected in the DiabCare BIS. The performance of the diabetes team is compared with the gold standards of the St. Vincent Declaration Program. The evaluation of the level of quality should cover the structure (housing, human resources, equipment, logistics) and the process (the way the care is organized, from the first call to the treatment plan; the annual measurements of indicators, HbA1c, blood pressure, etc.; the way the treatment is initiated, use of antihypertensive drugs, cholesterol-lowering agents, etc.).

The DiabCare program was designed for those services not having a computer database but having access to computers. In 1991, the feasibility phase, integrating the information from 4000 patients of 29 centers in 19 European countries, was completed. After some minor modifications, it gained widespread adoption by centers and local, regional, and national diabetes task forces all over Europe.⁵⁻⁷

The DiabCare Feasibility Study⁵ demonstrated the achievements obtained by the implementation of local documentation compatible to the DiabCare Diabetes Data Set. It made possible the assessment of the quality of care and to install regional/national quality networks, along with establishing a standard documentation to be used in various healthcare settings in different countries.

A quality circle is a group of motivated and committed people acting as a structured forum to solve on-the-job problems affecting the quality of their work. Prerequisites for the constitution of the circle are the political awareness and the involvement of the decision-makers to get things going. The implementation of pilots or demonstration projects make clear what the benefits are and the economic cost.

The quality circle must select targets according to the local health requirements. The information gathered after

data collection, data aggregation, and analysis (Figure 58.3) of proper indicators (clinical, analytical, etc.) allows a local evaluation (internal comparison); then, sending the aggregated data in anonymous fashion to a server, the comparison with all the other teams sharing the network is possible (external comparison).

After all of this, the members of the local quality circle are in the situation to propose and debate measures for quality improvement. These measures are implemented in the following period and the evaluation of their effects will be then analyzed, following the scheme of continuous assurance and improvement (Figure 58.4).

The present authors' use of the DiabCare program, adapted to a net environment in a hospital-based outpatient consultation, has provided a variety of benefits, including Diabetes Data Set exploitation as a registry, diabetes-type characterization, assessment of self-blood glucose monitoring (SBGM) status, St. Vincent Declaration targets, treatment characterization, outcome for diabetic pregnancies, completeness assessment of medical records, cardiovascular risk factors, and identification of groups of patients at risk.⁸

On the basis of this information, a quality assurance circle on diabetes care has been operating in the present authors' center since then, following the protocol proposed by the EU Consortium DiabCare Quality Network, integrated in a comprehensive disease management program (the Optidiab System). A published report about the information provided by the annual evaluation (the 141 parameters of the DiabCare BIS) of >1000 subjects confirmed the burden of type 2 diabetes patients compared to type 1 diabetes patients undergoing intensive and specialized care on a regular basis.⁹

Interestingly, aggregated and compared data from the central server, integrating national centers from the European DiabCare Quality Network (22,000 patients), lead to the conclusion that the long-term metabolic outcome of patients under intensive management in European specialized centers is far short of achieving their desired goal (HbA1c < mean + four standard deviations [4 SD] of the nondiabetic population); aggregated HbA1c levels (Diabetes Control and Complication Trial [DCCT] adjusted) recorded at the annual evaluation were optimal for only 26.9% of cases, acceptable for 23.2%, and poor in the remaining 49.9% of subjects.¹⁰

The DiabCare program allows a simple registration procedure for collecting basic data from pregnant diabetic women; the system has also been demonstrated to be useful for limited evaluation of quality assurance in the broad field of diabetes and pregnancy.¹¹⁻¹³

DiabCare BIS for diabetes and pregnancy

One of the main recommendations of the St. Vincent Declaration was the following: "Achieve pregnancy outcome in diabetic women that approximates to that of nondiabetic

Diabetes	
Basic Information Sheet	
Implementation of the St. Vincent Declaration	
Internat. Centre: _____ Implementation of the St. Vincent Declaration	
Basic Patient Data N ⁺ : _____ Initials: ☐ ☐ Date of Birth: _____ Sex: M ☐ F ☐ 1st name last name IDDM ☐ NIDDM ☐ Other ☐ Diabetes since: _____ OAD since: _____ Insulin since: _____	
Reason for Consultation/ Admission Consultation ☐ Routine visit ☐ Stabilisation ☐ Complications ☐ Other ☐ or: Admission ☐ Newly diagnosed ☐ Pregnancy ☐ Emergency ☐	
Pregnancies Ending within last 12 months ☐ Normal ☐ Abortions ☐ Major malformat. ☐ Perinatal deaths ☐	
Risk Factors current status Smoker ☐ if yes: cig./day _____ Alcohol ☐ g/day _____	
Self Monitoring Self-monitoring ☐ Blood glucose (nr/week) _____ Urin glucose (nr/week) _____	
Education/ Diab. Pat. Org. Healthy eating ☐ Foot care ☐ Complications ☐ Self-monitoring ☐ Hypoglycemia. ☐ Self adjustment ☐ Member of a diabetic patient organisation ☐	
Measurements most recent value in the last 12 months Weight _____ kg Blood Press. _____ / _____ mm Hg Cholesterol _____ Height _____ cm BG _____ Creatinine _____ HDL-Cholest. _____ HbA _{1c} _____ % Microalbum. _____ Triglycerides _____ HbA _{1c} _____ % Proteinuria _____ Fasting ☐	
St. Vincent Targets Blindness ☐ if yes: occurred last 12 mo. ☐ End-stage renal fail. ☐ if yes: occurred last 12 mo. ☐ MI/CABG/Angiopl. ☐ if yes: occurred last 12 mo. ☐ Leg amput. ab. ankle ☐ if yes: occurred last 12 mo. ☐ Cerebral stroke ☐ if yes: occurred last 12 mo. ☐ Leg amput. bel. ankle ☐ if yes: occurred last 12 mo. ☐	
Symptoms last 12 months Postural hypotension ☐ Anginal chest pain ☐ Peripheral neuropathy ☐ Leg claudication ☐	
Examinations YES Examined last 12 months ☐ ☐ left right Photocoagulation last 12 months ☐ ☐ Cataract ☐ ☐ Retina seen ☐ ☐ – if yes: Maculopathy ☐ ☐ Retinopathy ☐ ☐ – if Rp.: Non-proliferative Rp. ☐ ☐ Preproliferative Rp. ☐ ☐ Proliferative Rp. ☐ ☐ Advanced diab. eye disease ☐ ☐ Visual acuity _____	FEET Examined last 12 months ☐ ☐ left right Normal vibration sensitivity ☐ ☐ Normal pin prick sensitivity ☐ ☐ Foot pulses present ☐ ☐ Healed ulcer ☐ ☐ Acute ulcer/gangrene ☐ ☐ Bypass/angioplasty ☐ ☐
Quality of Life Emergencies Hypoglycemia _____ (no/yr) Hypoglycemia _____ (no/yr) Sick leave _____ (??) Hospital days _____ (??)	
Management Diet only ☐ up to now from now on ☐ ☐ Biguanides Since _____ ☐ ☐ N ⁺ . of Insulin-Injections/day _____ Sulphonylureas Since _____ ☐ ☐ Insulin-pump ☐ ☐ Glucosid. inhibit. Since _____ ☐ ☐ Other treatment ☐ ☐	
Additional Treatment Hypertension ☐ Cardiac failure ☐ Isch. heart dis. ☐ Dyslipidaemia ☐ Nephropathy ☐ Neuropathy ☐ Other ☐	

Figure 58.1 Basic Information Sheet, DiabCare.

Figure 58.2 DiabCare data for windows.

women.” In consequence, WHO/IDF guidelines for care and management of pregnant diabetic women have been proposed by an invited group of international experts in the field.¹⁴

The document brought attention to the important differences in the provision of diabetes and obstetrical care in different European countries. Specifically, the relevance of intensive metabolic care before conception and during pregnancy and parturition and the needs of special training and education of the diabetic women contemplating pregnancy were addressed. For the purpose of developing the quality assurance program, a DiabCare BIS for diabetes and pregnancy was proposed by members of the WHO/IDF Working Group on Pregnancy Outcomes in the Diabetic Woman (Figure 58.5), with data fields addressing diabetes diagnosis, obstetrical history, prepregnancy counseling, status at entering the specialized interdisciplinary clinic, maternal and newborn outcomes, and reclassification after pregnancy.

The OBStetrical Quality Indicators and Data (OBSQID) Perinatal Aggregated Data (PAD) protocol, mainly focused on outcomes, represents a valid alternative proposed by the Quality of Care and Technologies Program, WHO–Europe, being exploited for epidemiological studies.

Blood glucose monitoring in diabetic pregnancies

Portable meters are used by healthcare workers and by patients. Because of their imprecision and variability, they should not be used for diagnosing diabetes and their value in screening must be limited.

SBGM is recommended for all insulin-treated patients. Glucose can be measured in whole blood, serum, or plasma, but plasma is recommended for diagnosis. Although red blood cells are freely permeable to glucose, the concentration of water in plasma is around 11% higher than that of whole blood; as a consequence, the glucose concentration in plasma is higher than in whole blood (being the hematocrit normal). The glucose concentration decreases with time in the assay tube because of in vitro glycolysis (on average by 5%–7%, or 0.6 mmol/L or 10 mg/dL/hour), which can be attenuated by inhibition of enolase with sodium fluoride used in combination with anticoagulants. Therefore, when plasma glucose is going to be analyzed, plasma should be separated from cells within 1 hour. Glucose is almost exclusively measured by enzymatic methods (hexokinase, glucose oxidase).

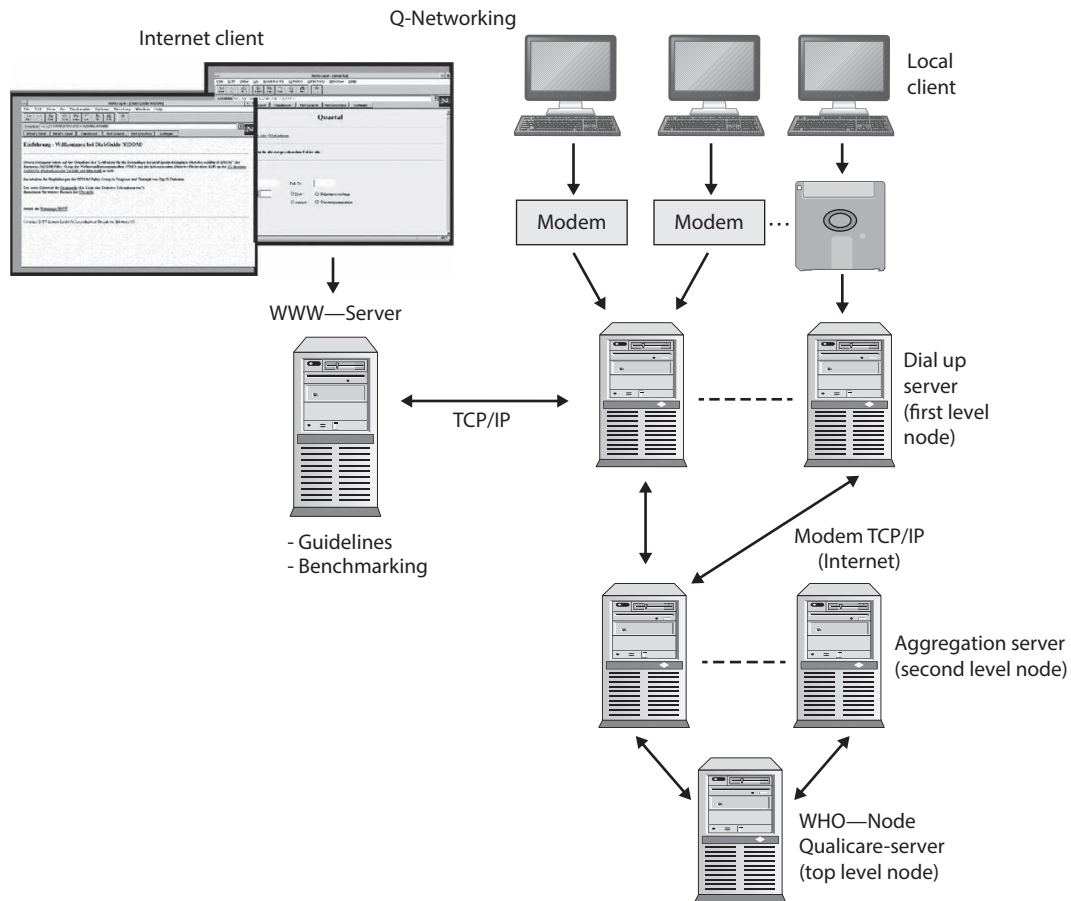


Figure 58.3 DiabCare Q-Net, system architecture.

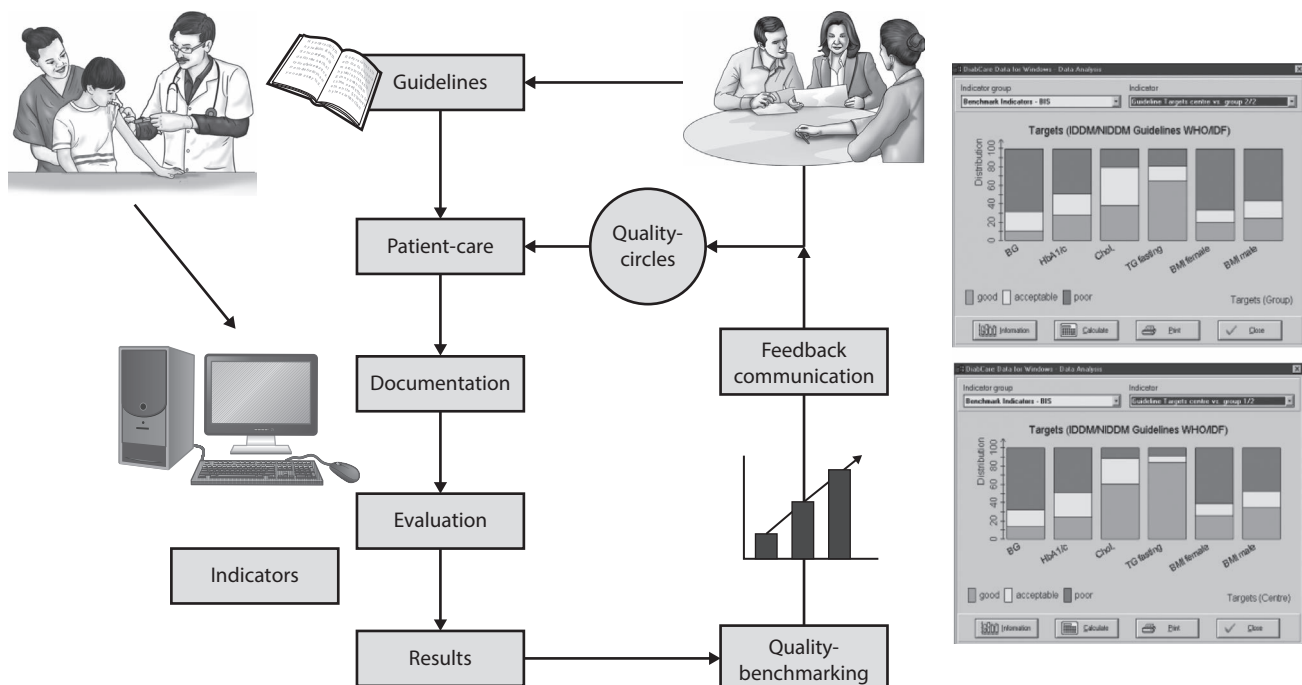


Figure 58.4 Operation of the DiabCare quality circle.

Basic Information Sheet for Diabetes and Pregnancy			
Data Set Number:		Country:	Centre Name:
Treating Physician:		Date of record:	
Basic Personal Data			
Family Name:		Given Name:	Date of Birth:
Residence: ☐ Urban ☐ Rural	Distance from Clinic (km):		Single: ☐ Yes ☐ No
Education:			
☐ None ☐ Primary ☐ Secondary ☐ University			
Diabetes Diagnosis			
DM Diagnosis:		Diagnosis Based on:	
☐ DM-Type 1 ☐ GDM		☐ NDDG criteria	
☐ LADA ☐ Secondary-DM		☐ IADPSG criteria	
☐ DM-Type 2		☐ Other	
Date:		Gestational Week:	
Past Obstetrical History			
Previous Pregnancies:	Induced Abortions:		
Total Live Births:	Stillbirths:	Early Infant Mortality:	
Spontaneous Abortions:	Pregnancy with Diabetes:	Late Infant Mortality:	
Deaths in First Year:			
Born with Major Malformation:			
Pre-Pregnancy Counselling			
Pre-Pregnancy Counselling: ☐ Yes ☐ No		HbA1c: %	
Structured Information: ☐ Yes ☐ No		DCCT/UKPDS criteria (standard): ☐ Yes ☐ No	
Microalbuminuria: ☐ Yes ☐ No	Proteinuria: ☐ Yes ☐ No	Date of Referral for Index Pregnancy:	
mg/24h	mg/24h		
Booking			
Date of First Visit to the Specialist:		Pregnancy Advised Against: ☐ Yes ☐ No	
Last Menstruation Period:		Planned Pregnancy: ☐ Yes ☐ No	
Conception:		Booking:	
HbA1c: %		HbA1c: %	
DCCT/UKPDS criteria (standard): ☐ Yes ☐ No		DCCT/UKPDS criteria (standard): ☐ Yes ☐ No	
Microalbuminuria before pregnancy: ☐ Yes ☐ No		Proteinuria before pregnancy: ☐ Yes ☐ No	
mg/24h		mg/24h	
Previous Retina Laser Treated: ☐ Yes ☐ No			
Around Conception:			
Insulin: ☐ Yes ☐ No OAD: ☐ Yes ☐ No Lowering BP Med: ☐ Yes ☐ No ACE Inhibitor: ☐ Yes ☐ No			
Mother			
Gestational Week of Termination:	Third Trimester	Severe Hypos:	
Weight Gain in Pregnancy:	HbA1c: %	Ketoacidotic Episodes:	
Self Measure BG/wk Last Trimester:	DCCT/UKPDS: ☐ Yes ☐ No	Acute Urinary Tract Infections:	
Progress of:		Chronic Hypertension: ☐ Yes ☐ No	
☐ Retinopathy: ☐ Yes ☐ No		☐ Chronic HT and PIH: ☐ Yes ☐ No	
☐ Nephropathy: ☐ Yes ☐ No		☐ Pregnancy Induced Hypertension (PIH): ☐ Yes ☐ No	
GDM: ☐ Yes ☐ No			
Preconceptional:			
First Trimester:			
Second Trimester:			
Third Trimester:			
Birth			
Stillbirth: ☐ Yes ☐ No			
Abortion:		Labour:	
☐ Induced		☐ Spontaneous: ☐ Yes ☐ No	
☐ Spontaneous		☐ Instrument Used: ☐ Yes ☐ No	
		☐ Induced: ☐ Yes ☐ No	
		☐ Cesarean Section: ☐ Yes ☐ No	
Maternal Discharge:			
☐ Alive			
☐ Dead			
Newborn			
Male: ☐ Female: ☐	Neonatal Weight: g	Length: cm	Head circle: cm
Apgar (1 min):		Apgar (5 min):	
		Discharge: ☐ Healthy ☐ Ill ☐ Dead	
Pathologies:			
☐ Obstetric Trauma: ☐ Yes ☐ No		☐ Neonatal Asphyxia: ☐ Yes ☐ No	
☐ Hyperbilirubinemia: ☐ Yes ☐ No		☐ Severe Hypoglycemia: ☐ Yes ☐ No	
☐ Fetal Distress: ☐ Yes ☐ No		☐ Hyaline Membrane Disease: ☐ Yes ☐ No	
☐ Severe Hypocalcaemia: ☐ Yes ☐ No		☐ Polycythemia: ☐ Yes ☐ No	
Neonatal Malformations:			
☐ Cardiovascular: ☐ Yes ☐ No		☐ Genitourinary: ☐ Yes ☐ No	
☐ Neurotube: ☐ Yes ☐ No		☐ Skeletal: ☐ Yes ☐ No	
		☐ Gastrointestinal: ☐ Yes ☐ No	
		☐ Other: ☐ Yes ☐ No	
Feeding: ☐ Breast ☐ Bottle			
Reclassification			
Has the Type of Diabetes Been Reclassified? ☐ Yes ☐ No			
Postpartum:		After 5 years:	
☐ Normal GT		☐ Normal GT	
☐ DM-Type 1		☐ DM-Type 1	
☐ DM-Type 2		☐ DM-Type 2	
☐ LADA		☐ LADA	
☐ Other		☐ Other	

Figure 58.5 DiabCare Basic Information Sheet for diabetes and pregnancy. (Adapted from Tamás, G. et al., *Av. Diabetol.*, 5, 137, 1992; de Leiva, A. and Hernando, M.E., *Diabetes Care*, 32(Suppl. 2), S211, 2009.)

For plasma glucose, a coefficient of variation $<2.2\%$ is recommended as a target for imprecision.

The evaluation of SBGM devices may be misleading; in general, several units should be tested to explore interdevice variability. The evaluation should include the analysis of the mean difference of the device reading, with respect to a reference procedure at low, medium, and high blood glucose concentrations. Other items of the evaluation will include customer acceptability (size, weight, portability, calibration, duration of a test performance, economic cost). Then, a validation protocol using an adequate sample size of recruited patients will follow, covering a wide range of blood glucose levels from the hypoglycemic range to extreme hyperglycemia.

The utilization of memory meters has shown that patients often make incomplete recordings of their daily blood glucose profiles (inaccurate readings, omission of outliers, false

reports not recorded in the memory of the meter), usually depicting a trend toward correcting results of readings.^{15,16}

Of course, adequate training, visual acuity, hypoxia, altitude, hemolysis, hematocrit, hypertriglyceridemia, adequate sample volume,¹⁷ and other technical elements can influence the results. Reinforcing patient education at regular clinic visits, evaluating his or her technique, and frequent comparison of SBGM profiles with concurrent laboratory blood glucose analysis will assess the reliability of patient reports.

Many different brands of meters are commercially available. They use strips containing glucose oxidase or hexokinase; some meters contain a porous membrane that separates erythrocytes, the analysis being carried out in plasma. The meters provide a digital readout using reflectance photometry or electrochemistry for the measurements of glucose concentration.

Table 58.1 Blood glucose targets

The American Diabetes Association and the American College of Obstetricians and Gynecologists recommend the following blood glucose targets: <95 mg/dL at fasting, <140 mg/dL at 1 hour after meals, and <120 mg/dL at 2 hours after meals.

There is a wide variability in the performance of the different meters and the level of imprecision remains high. The American Diabetes Association (ADA) goal of analytical deviation remains <5% from reference values.^{18–20}

SBGM should be performed at least four times per day in patients with type 1 DM. It has been demonstrated that monitoring with a lower frequency than this is associated with deterioration of glycemic control. In both GDM and pregestational diabetes, it is usually recommended to measure blood glucose levels at fasting and 1 or 2 hours after meals (Table 58.1).^{21,22}

Noninvasive or minimally invasive continuous monitoring of blood glucose is a high priority (both to detect unsuspected hypoglycemia and as a further step in the development of an artificial pancreas), allowing automatic measurement of blood glucose and adjustment of insulin administration (Figure 58.6). The method for sampling in minimally invasive systems takes advantage of the correlation between the concentration of glucose in the interstitial fluid and in blood.^{23,24} Whereas microdialysis systems are inserted

subcutaneously, reverse iontophoresis uses a low-level electrical current, which by electro-osmosis moves glucose across the skin, with the glucose concentration measured by a glucose-oxidase detector.^{25,26} Total noninvasive technology for glucose sensing, including techniques of near-infrared spectroscopy, light scattering, and photoacoustic spectroscopy, is in progress. It is anticipated that important progress in these methods for noninvasive or minimally invasive glucose monitoring will be made in the near future.

Impact of advanced technologies in the quality of care of diabetic pregnancies

Telemedicine in pregnancy complicated by diabetes: Overview on quality care

One of the first experiences of telemedicine (TM) applied to diabetes management was the DIACRONO device, a micro-computer that allowed data interchange between doctor and patient; it already included the function of downloading glucose data from the glucometer.²⁷ The same group of researchers developed DIABTel, which is made possible by remote supervision and teleconsulting to improve patient–physician communication²⁸ and to provide decision support in diabetes management.²⁹ Following initiatives used Internet: TIDDM,³⁰ M2DM,³¹ all of them EU Projects, which, finally,

Date/Time	Optimal accuracy criteria			Sensor				Meter			
	No. of paired sensor Mtr readings	Correlation coefficient (r)	Mean absolute difference (%)	No. of readings	Average (mg/dL)	STO (mg/dL)	Sensor range (mg/dL)	No. of Readings	Average (mg/dL)	STO (mg/dL)	Meter range (mg/dL)
13-Nov-00 x	6	.30	.29	154	164	67	40–271	6	159	32	100–204
14-Nov-00	8	.97	11	288	107	39	45–202	8	102	46	49–183
15-Nov-00	10	.95	13	288	164	59	48–294	10	129	73	43–283
16-Nov-00 x			0	118	202	49	80–271	1	179	0	179–179
All days	25	.87	16	848	150	63	40–294	25	130	60	43–283

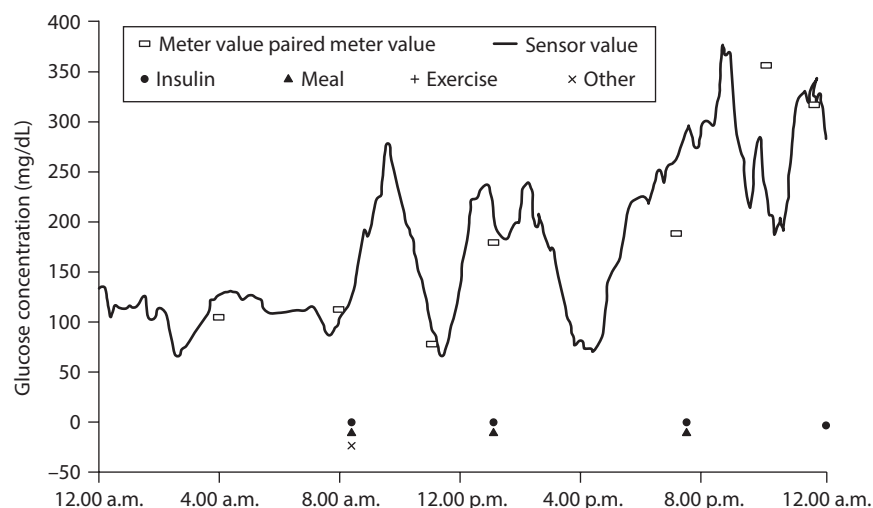


Figure 58.6 Registry of continuous glucose monitoring in interstitial subcutaneous tissue.

integrated for the first time, continuous glucose monitoring (CGM) into a smart TM platform and various predictive algorithms with positive results in glycemic control and glucose variability (EU INCA Project).^{32,33}

A recent systematic review and meta-analysis has investigated the impact of TM on the management of diabetes (4207 patients, type 1 or 2). TM was associated with a statistically significant decline in HbA1c (mean difference -0.44%). Low density cholesterol level (LDL-c) was reduced in 6.6 mg/dL, just a tendency to reduce body mass index (BMI), and there were no changes in either systolic or diastolic blood pressure.³⁴

The use of TM can facilitate the management of diabetic pregnancies in multiple aspects:

1. Education of patients and relatives
2. Teleconsultations (e-mail, online text messages, mobile phones, etc.)
3. Videoconferences, excellent tools for training and communication to multiple patients
4. Greater involvement of other healthcare professionals (dietitians, midwives), saving physicians' time, without affecting the quality of care³⁵
5. Reducing the number of visits to diabetes clinic and emergency department

Having real-time access to medical devices can improve decision-support tools with immediate feedback to patients. A personal assistant (PA) integrated in a portable device such as a smartphone is able to communicate different medical devices and/or sensors in a personal wireless network.³⁶ The system is able to support diabetes care in a distributed and ambulatory environment.³⁷ The mobile application can provide advice from automatic processing tools based on monitoring data as well as expert feedback to patients. The whole system has been successfully tested in two randomized and crossover clinical experiments with type 1 diabetic patients showing that the wireless PA joined to the TM system allows better glycemic control in insulin pump-treated diabetic patients.³⁸

Continuous subcutaneous insulin infusion

Continuous subcutaneous insulin infusion (CSII) and multiple doses of insulin (MDI) are both safe and valid treatments for women with type 1 diabetes during pregnancy.^{39,40} Nevertheless, the main predictors of glucose optimization in CSII therapy are high HbA1c levels before CSII, pregestational care, younger age, and the use of more basal segments over the daily insulin profile.⁴¹

Closed-loop insulin delivery

In recent years, the acceptable accuracy of continuous glucose sensing in association with the model predictive control (MPC) algorithm has been demonstrated; overnight closed-loop insulin delivery under these premises can be used safely in pregnancy.⁴² Nevertheless, large multicenter randomized studies are needed to confirm the benefits of closed-loop insulin delivery in comparison with sensor-augmented pump therapy.

So far, clinical trials show that closed-loop insulin delivery in diabetic women during pregnancy and out of pregnancy improves stability of glucose control at night and prevents the "dawn phenomenon," but delayed insulin action at meal-time results in hyper-/hypoglycemia. Therefore, in spite of the great research effort invested into the development of closed-loop control algorithms, their continuous ambulatory utilization is still far from being a short-term reality; patient safety reasons for this initiative have also been argued.

The telemedical artificial pancreas (TAP) is built on two interlinked loops. The "personal loop" allows wireless communication between the PA—a personal device assistant-based smart assistant—an insulin pump, and a CGM device. The "remote loop" connects the diabetic subject to the healthcare professional via the PA and its wireless connection to the telemedicine central server (TMCS). The platform implies two control modes:

1. The patient decides changes in the insulin pump program by using the information coming from the glucosensor (*free mode*).
2. The patient gets advice, through the PA, on the insulin bolus before each main meal (*advisory mode*). The patient uses the PA to register and transfer data related to timing, pre- and postprandial glucose excursions, amount of ingested carbohydrates, and additional relevant information (e.g., previous exercise). From this information, the ad hoc algorithm computes the corresponding insulin dose that has to be approved by the physician, through the web interface, before it is shown to the patient (Figure 58.7). The patient uses the PA to get results of the proposed insulin bolus and decides to follow it or not.⁴³

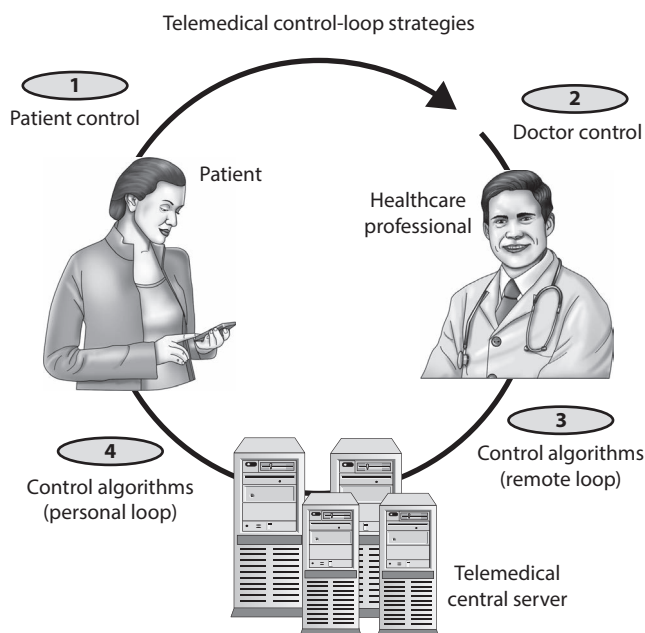


Figure 58.7 Telemedical artificial pancreas. (Adapted from Telemedical Artificial Pancreas; EC-INCA Project: Gómez, E.J. et al., *IEEE Trans. Inf. Technol. Biomed.*, 12(4), 470, 2008; de Leiva, A. and Hernando, M.E., *Diabetes Care*, 32(Suppl. 2), S211, 2009.)

The system has been, so far, technically validated and a clinical pilot has been also satisfactorily carried out. A multicenter randomized ambulatory crossover study is already in process.

Very recently, the safety and effectiveness of a bihormonal, automated pancreas ("bionic pancreas"), allowing the precise delivery of insulin and glucagon, have been compared with insulin pump (control). The clinical experiment was validated for 5 days in 20 adults and 32 adolescents with type 1 diabetes. The bionic pancreas achieved improved mean glycemic levels with less frequent hypoglycemic episodes.⁴⁴

Glycated hemoglobin (HbA1c) and glycation of human serum albumin

More than 40 years ago, it was observed that normal adult hemoglobin could be separated by chromatographic procedures into major and various minor components. In one of the minor components—HbA1c—glucose was attached, nonenzymatically, to the terminal N-valine of the beta chain of HbA0. In the following years, numerous assays were developed to measure HbA1c levels.

The average lifespan of erythrocytes is 100–120 days. Measuring HbA1c offers an accurate estimation of the average blood glucose concentration of the past 2–3 months. HbA1c is used as an integrated estimation of mean glycemia and as a marker of risk for the development of diabetes complications.

At present, there are more than 30 HbA1c assay methods available. Certain methods quantify HbA1c based on charge differences of the glycated components (cation exchange chromatography, agar gel electrophoresis). Other methods analyze structural differences between glycated and nonglycated components (affinity chromatography, immunoassay). In addition, various methods quantify total glycated hemoglobin, including HbA1c and other hemoglobin–glucose adducts.

In 1996, the American Association of Clinical Chemists (AACC), in collaboration with the ADA, established the National Glycohemoglobin Standardization Program (NGSP). It was decided to adopt the high-performance liquid chromatography (HPLC) reference method used in the DCCT (Bio-Rex 70; between run coefficient of variation [CV] <3%), as the designated comparison method.

The UKPDS incorporated the same standardization method; therefore, its HbA1c reports were compatible with those of DCCT. More than 90% of U.S. laboratories, and many others worldwide, are using this procedure for standardization purposes.⁴⁵

Any condition that shortens erythrocyte survival (hemolytic anemia, acute blood loss) falsely lowers HbA1c test results; in contrast, iron-deficiency anemia increases the value. Glycation may also vary between patients with similar capillary blood glucose levels and appears to be lower in subjects with a higher BMI.

Several hemoglobinopathies interfere with some assay methods; the results can be falsely increased or decreased; non-hemoglobin-based methods for assessing long-term glycemic control may represent useful alternatives in these circumstances.⁴⁶

European guidelines have recommended the classification of blood glucose control by the number of SD; the experimental value is from the nondiabetic mean for the particular assay.⁴⁷

The International Federation of Clinical Chemistry (IFCC) has organized a working party to develop a scientifically based method of the production of a primary reference. Electrospray ionization mass spectrometry (ESIMS) has been demonstrated to be a precise measurement of HbA1c, in particular glycation of the beta chain, which has been proposed as a robust procedure for calibration purposes. In a protocol performed with 1022 patients, the comparison of the ESIMS with the ion-exchange chromatographic procedure showed excellent agreement, with values, on average, 0.7% lower with ESIMS. The comparison with DCCT-corrected ion-exchange values gave good agreement, with ESIMS showing an overall lower value of mean 0.4%.⁴⁸

There is a general agreement that the new mass-spectroscopy-based method appears to be more accurate and to reflect "true" HbA1c. It yields normal (nondiabetic) values that are significantly lower than those used by the NGSP, DCCT, and UKPDS (3%–5% vs. 4%–6%).

The Ames DCA 2000 Analyzer measures HbA1c by an agglutination inhibition immunoassay, allowing results in 6 minutes with 1 mL of blood. The Ames DCA 2000 analyzer offers reliable results, although showing a trend to lightly underestimate the results in comparison with HPLC.⁴⁹ This analyzer gave valid and reliable results when operated by nonmedical personnel. The Primus CLC330 provides an HPLC near-patient HbA1c method, comparable in precision and accuracy to the Ames DCA 2000 analyzer.⁵⁰ Near-patient testing for HbA1c has practical clinical use in the diabetes clinic, avoiding the need for a second appointment and allowing immediate changes in therapy.

About using HbA1c for the diagnosis of diabetes mellitus

In 2010, the ADA introduced a value of HbA1c equal or superior to 6.5% as diagnostic criteria of diabetes,⁵¹ primarily based upon the increased accuracy and reliability of the improvement of A1c assays through the NGSP. A1c correlates well with both mean glucose concentration⁵² and complications of diabetes. Nevertheless, the new recommendations acknowledge that a cutoff for A1c equal or above 6.5% classifies one-third fewer individuals as having diabetes in comparison with a fasting plasma glucose (FPG) value equal or above 126 mg/dL. Some advantages of the estimation of A1c include the following: (1) fasting is not needed, (2) A1c is not subjected to acute perturbations (stress, exercise, diet, etc.), and (3) A1c can be used for both diagnosis and initiation of

diabetes monitoring. On the contrary, (1) standardization of A1c assay is poor; (2) A1c depicts important differences in various ethnic groups; (3) the cost is elevated when compared to glucose assay; (4) A1c levels vary not only according to glycemia but also according to the erythrocyte turnover rate (anemia, hemoglobinopathies, malaria, etc); (5) A1c levels of 6.0%–6.5% do not predict diabetes as effectively as FPG and 2-hour OGTT; and (6) using A1c may delay the diagnosis of DM in more than 50% of cases.⁵³

NGSP Network

The NGSP was implemented to standardize HbA1c results to those of the DCCT/UKPDS. There have been considerable variations in the procedure for reporting glycated hemoglobin; in addition, an important variability among values reported in each category was displayed, which was associated with confusion in clinical practice. The DCCT tried to avoid the variability among results by having all analyses of HbA1c performed in a single laboratory. Then, the AACC decided to standardize the HbA1c assay to facilitate that all clinical laboratories are able to compare their own results with those of DCCT/UKPDS. For this purpose, a network of NGSP consisted in a central primary reference laboratory (CPRL), using the DCCT/EDIC Bio-Rex 70 HPLC method, additional primary reference laboratories, using the same method, and seven secondary reference laboratories (SRLs) using commercial methods (ion-exchange HPLC, immunoassay, boronate-affinity HPLC, capillary electrophoresis).⁵⁴

The IFCC also created a working group to develop an internationally accepted reference method and HbA1c materials for the assay. Each laboratory of the IFCC Network runs one of the two approved IFCC methods (HPLC–mass spectrometry or HPLC–capillary electrophoresis). Results obtained by the IFCC method correlates quite well with NGSP/DCCT results.

ADA, EASD, and IDF reached the agreement that laboratories should report an estimated average glucose (eAG).⁵⁵ A linear relationship was established between the HbA1c and mean blood glucose, but the observation of too much variability in the HbA1c/mean BG relationship did not make the report of eAG advisable (it has not been accepted outside the United States).

A new International Consensus in 2010 indicated that HbA1c should be reported in both DCCT units (%HbA1c) and NGSP units (millimoles/M).⁵⁶ After all of these efforts, the quality of HbA1c test meets the clinical needs.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study compared associations of maternal glucose and A1c with adverse outcomes. A1c was measured by an HPLC method (Biomen HA 8140 instrument). The coefficient of variation ranged from 2.8% to 5.0% across the range of A1c values. For external quality control, the Central Laboratory participated in the European Reference Laboratory Program, which allows standardization of DCCT values, and the U.K. National Glycation

Standardization Program. The mean (SD) A1c result of 21,064 HAPO Study participants was 4.79 (0.40)%.⁵⁷

In a recently published study of 335 gravidas who received a 3-hour, 100 g OGTT at 24–32 weeks, it was discovered that HbA1c concentrations gradually increased in diet-treated and insulin-treated GDM gravidas compared with non-GDM gravidas. The HbA1c value corresponding to an FPG of 5.1 mmol/L (diagnostic of GDM) was 2 mmol/L (0.2%) higher if sampling occurred at 29–32 vs. 24–28 weeks of pregnancy, indicating that HbA1c varies with gestational age.⁵⁸ Various other reports have recommended to incorporate HbA1c in the diagnosing criteria. The WHO considers that HbA1c of 48 mmol/mol (6.5%) and above is diagnostic of DM. Individuals with HbA1c values below such a cut-off may still have diabetes; abnormal Hb variants, anemia, altered lifespan of the red cell, aging, and ethnicity, among other variables, ought to be taken into consideration. Clinical judgment is required for each individual to avoid inappropriate exclusion or inclusion in the category of diabetes.

Glycated serum proteins

Mostly albumin and other serum proteins undergo the process of glycation. Glycated albumin (GA) is a ketoamine formed via nonenzymatic glycation of serum albumin. The turnover of serum albumin depicts a half-life of 25 days; GA provides an index of a mean glycemic level of a shorter interval than HbA1c. The fructosamine assay is the most widely used method for estimating glycated serum proteins.

Nevertheless, although fructosamine levels correlate with HbA1c levels within a population, transference cannot apply for individual values.⁵⁹ Also, changes in serum proteins affect the readings of fructosamine⁶⁰; the technique is unreliable in diabetic patients with renal failure,⁶¹ liver cirrhosis, and nephrotic syndrome.⁶²

GA can be used for patients with anemia or hemoglobinopathies. It can be also used to estimate the effectiveness of treatment before starting or changing medications for diabetic patients. As GA is potentially an atherogenic protein, GA measurement may be included in the routine protocol to screen for both diabetes and atherosclerosis.⁶³

Assessment of the effectiveness of SBGM in diabetic pregnancies

Various randomized controlled trials (RCTs)^{64–68} and case series studies^{69–72} carried out in either diabetes or obstetrics departments of university hospitals have evaluated the clinical effectiveness of SBGM in women with GDM or diabetic pregnancies. Blood glucose and HbA1c determinations, as well as maternal and fetal outcomes, were recorded. Some studies examined the costs of hospital care and home monitoring and compared the costs for a control group receiving standard care. The largest of all protocols

included a population of 153 women with GDM in the experimental group and 2153 nondiabetics in the control group. The main goal of the case series studies was to assess the feasibility of managing pregnant women at home using SBGM. There was general agreement that women were able to achieve satisfactory blood glucose profiles at home using SBGM; hospital utilization was lower, and infant birth weights and indicators of macrosomia were also more favorable in those women. Main findings from the RCT demonstrated that patients with type 1 DM managed by SBGM at home obtained similar results regarding glycemic control to those patients under intensive control in the hospital. Maternal and fetal outcomes were also similar in both groups. Women preferred lower use of hospital and home management with SBGM. In particular for GDM, monitoring blood glucose after meals, rather than before, contributed to better metabolic control and better fetal outcomes (there were fewer cesarean sections for cephalopelvic disproportion, fewer cases of macrosomia and large-for-gestational-age infants, and fewer episodes of neonatal hypoglycemia). In addition, women who utilized SBGM were less likely to require hospital admission, leading to a substantial cost saving.

Impact of the Hyperglycemia and Adverse Pregnancy Outcome Study in the quality of care of diabetic pregnancies

The HAPO Study, a prospective, blinded, multinational, observational study, published in 2008, investigated almost 25,000 pregnancies.⁷³ The study demonstrated a continuous association between elevated maternal blood glucose concentrations and the risk of pregnancy complications (large for gestational age, preeclampsia, primary cesarean section, neonatal hypoglycemia, elevated cord blood serum C-peptide, premature delivery, and hyperbilirubinemia).

The International Association of Diabetes and Pregnancy Study Group (IADPSG) developed, after the publication of the HAPO Study, a new strategy for detection and diagnosis of hyperglycemic disorders in pregnancy in two phases. The first is detection of women with overt diabetes not previously diagnosed, measuring FPG, A1c, or random plasma glucose on all or only on high-risk women. One or more values equaling or exceeding the following thresholds—7 mmol/L (126 mg/dL), 6.5% (DCCT/UKPDS standardized), and 11.1 mmol/L (200 mg/dL) (it should be confirmed by FPG or A1c)—will make the diagnosis of overt diabetes in pregnancy, and the woman will be treated as with preexisting DM. If results are not diagnostic of overt diabetes and FPG equals or exceeds 5.1 mmol/L (92 mg/dL), the diagnosis of GDM will be made. If FPG concentration is lower than 5.1 mmol/L (92 mg/dL), the woman will be investigated again in the second phase. The second phase is a 75 g OGTT

at 24 weeks of pregnancy, performed after an overnight fast. Overt diabetes will be diagnosed if FPG equals or exceeds 7.0 mmol/L (126 mg/dL) and GDM if one or more values equal or exceed the following threshold values: FPG, 5.1 mmol/L (92 mg/dL); 1-hour plasma glucose, 10.0 mmol/L (180 mg/dL); and 2-hour plasma glucose, 8.5 mmol/L (153 mg/dL).⁷⁴ Accepting IADPSG recommendations means more accurate and timely diagnosis of pregestational diabetes and of GDM and probably will double the frequency of pregnant women with diabetes. The economic impact of this new approach deserves thorough investigation and is likely to differ across countries.⁷⁵

The WHO in a recent report has confirmed the increased prevalence of GDM accepting the new IADPSG criteria, which has implications for health services and human and material resources. The IDF estimates that the global prevalence of hyperglycemia in pregnancy in women aged 20–49 years is 16.9%. Some health services throughout the world may experience difficulties in meeting these demands; therefore, it is important for each health service to assess the burden of diagnosing and optimally treating pregnancy complicated by diabetes before adopting the convenient decision to implement programs to test and treat the condition.⁷⁶

Quality of life in women with GDM: The Italian DAWN Pregnancy Study

The diagnosis of diabetes is a cause of anxiety, particularly in the case of women in pregnancy. IDF has promoted the Diabetes Attitudes, Wishes and Needs (DAWN) study to assess the quality of life of diabetic patients and the satisfaction of healthcare professionals involved in the management of diabetes.^{77,78}

The Italian Dawn Pregnancy Study represents the first initiative of this kind carried out in the area of diabetes and pregnancy. Ten specialized Italian centers with experience in the management of diabetic pregnancy collaborated in the investigation. Recruited women were 198 Italians and 88 immigrants (from 27 nationalities) who answered a survey containing 51 items.⁷⁹

Most women (94%) responded they were happy about the quality of care provided in the different diabetes centers. The main reasons for anxiety during pregnancy included the fear of congenital malformations and the risk for future diabetes in the newborn, as well as the potential negative consequences in babies related to the insulin administration to the mother. The majority of women (73%) expressed their perception of suboptimal cooperation between gynecologists and diabetes specialists. The study revealed the effort of immigrants (particularly Muslims) to change eating habits and related religious recommendations about diet in pregnancy. A main recommendation derived from the investigation was to optimize the communication between healthcare personnel and patients, as well as between gynecologists and diabetes specialists.

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59 Early pregnancy loss and perinatal mortality

Kinneret Tenenbaum-Gavish, Anat Shmuely, and Moshe Hod

Introduction

Diabetes is one of the most prominent medical disorders complicating pregnancy, probably affecting 1 out of 250 pregnant women.^{1–3} Gestational diabetes occurs in up to 18% of all pregnancies,^{4–7} and it is estimated that approximately 10%–15% of diabetic pregnancies are due to pregestational diabetes.^{8,9} Furthermore, diabetes is considered a major risk factor for congenital malformations, stillbirth, and neonatal death—all constituting increased perinatal mortality (PNM).^{2,5,10,11}

Achieving the desired level of glycemic control prior to and during pregnancy is crucial in order to reduce PNM.^{12–17}

Definitions

Perinatal mortality

PNM still remains the standard measure to evaluate adverse pregnancy outcome. There is a considerable difficulty in estimating PNM due to numerous systems used and substantial differences in definitions of PNM. Even the World Health Organization's (WHO) reports do not all follow the same definitions.^{18–20} The American National Vital Statistics System and the British Confidential Enquiry into Maternal and Child Health (CEMACH) both use gestational age as the basis for calculation of stillbirth and neonatal death but differ in the referred gestational age (20 vs. 24 weeks of gestation).² In the Netherlands, gestational age >24 weeks and/or birth weight > 500 g were used and a French survey used either 22 weeks of gestation or 500 g at birth for their study.^{17,19} This variance between reports makes international comparisons somewhat more difficult and may hinder identification of temporal or geographic trends. Furthermore, little can be said about the standard of care that is reflected by these adverse pregnancy outcome measures.

Perinatal mortality—this definition of PNM has been adapted internationally:

$$\frac{\text{Stillbirths} + \text{Deaths from 0 to 6 days of age}}{\text{All live births} + \text{Stillbirths}} \times 1000$$

Live birth was defined by the WHO as “The complete expulsion or extraction of a product of conception, irrespective of the duration of pregnancy, which after such separation breathes or shows any evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut, or the placenta is attached, each product of such a birth is considered live born.”¹⁸

Common causes of perinatal mortality

The cause of death can be identified in 65%–75% of cases, depending on the expertise of the multidisciplinary team involved.²¹

1. *Stillbirth or fetal death*—Fetal death was defined as an involuntary loss in which the fetus (>20 weeks of gestation) showed no evidence of life (i.e., no heartbeat or respiration) on delivery.²² In other studies, stillbirth is the death of a fetus >24 or 28 weeks of gestation.⁴ There are considerable variations regarding the rates of stillbirth in different countries. The WHO's report on the topic of stillbirths (defined there at or after 28 weeks of gestation) reported that two-thirds of stillbirths occur in Southeast Asia and Africa and 55% occur in rural families from these areas. The stillbirth rate has declined worldwide by 14% from 1995 to 2009, representing an annual decline of 1.1% per year. The rate of decline in the African region is 0.7% compared to 3.8% in the Western Pacific region.²³ Stillbirth may account for up to 50% of cases of PNM and the underlying cause may remain obscure depending on resources applied.²⁴ Causes for stillbirth are generally grouped into three categories: fetal, placental, and maternal (Table 59.1, reference 21).
2. *Neonatal death*—The death of a live-born infant before the age of 28 days. Neonatal death can be divided into early and late neonatal deaths: early neonatal death is defined as the death of a live-born infant during the first 7 days after birth. Late neonatal death is the death of a live-born infant after 7 days but before 29 days of birth.^{2,25,26}

Table 59.1 Categories of stillbirth

	Fetal	Placental	Maternal	Other
Percentage of cases (%)	25–40 e.g., chromosomal anomalies, congenital malformations, infections, hydrops	Up to 25 e.g., placental abruption, cord accidents, infections, fetomaternal hemorrhage, placenta previa, etc.	5–10 e.g., hypertension, vascular disease, thrombophilia, trauma, substance abuse, etc.	Unknown Combined causes, e.g., maternal illness causing placental abruption or insufficiency

Source: Wood, S.T. et al., *Diabetes Care*, 23, 1752, 2000.

Neonatal death is largely attributed to four factors: preterm delivery, infections (mainly sepsis and pneumonia), birth asphyxia, and fetal anomalies affecting the neonatal period.²⁵

Early pregnancy loss

Early pregnancy loss is an indirect measure related to quality of care before and during early pregnancy. Early pregnancy loss or spontaneous abortion refers to pregnancy loss at less than 20 weeks of gestation in the absence of elective medical or surgical measures to terminate the pregnancy.²⁵

Etiology of PNM

Diabetes affects the metabolism of all nutrients (carbohydrates, fatty acids, and proteins), glucose being the most prominent. Glucose and those other metabolic fuels operating at the different stages of pregnancy may account for the multitude of pathologies inflicted upon the offspring of the diabetic mother. These pathological conditions range from congenital malformations and intrauterine fetal death to macrosomia, respiratory distress, and hyperbilirubinemia. Poor metabolic control may also induce alternations in levels of fatty acids and amino acids. This provides an altered environment in which the embryo and fetus of the diabetic mother may be exposed to changes in gene expression and increased teratogenesis.^{27,28}

Hyperglycemia by itself is involved in the pathogenesis of factors contributing to PNM throughout the entire length of pregnancy.²⁹ In vitro, high glucose levels generate free oxygen radicals that are linked to mechanisms of cellular damage.^{27–30} Not surprisingly, the congenital malformation rate (which largely contributes to the higher rate of PNM in pregnancies complicated by diabetes) was found to be inversely related to maternal age and directly related to the level of glycemic control during early pregnancy.^{31,32} Good glycemic control brings about adequate levels of glucose and insulin and is therefore associated with lower levels of ketones. It was suggested that maternal ketosis plays an important part in the occurrence of congenital malformations in the fetus.³³

Later in pregnancy, maternal hyperglycemia is translated into fetal hyperplasia of pancreatic islet cells and hyperinsulinemia. Pedersen et al.^{34,35} linked this to early neonatal hypoglycemia. A series of studies by Salvesen et al.^{36,37} demonstrated that hyperinsulinemia is related to cord blood acidemia and hypoxemia. It is suggested that hypoxemia and acidemia are related to increased rates of stillbirth and neonatal death observed in the diabetic population. Furthermore, insulin has an anabolic effect on muscle and adipose tissue linked to fetal macrosomia.^{37,38} Macrosomia in its turn is related to increased risk of PNM and shoulder dystocia.³⁹

PNM in the diabetic population

Although steps forward in modern obstetrics allow early detection of congenital malformation and assessment of fetal well-being, PNM rates in the diabetic population still remain up to five times higher than those of the general population.^{3,29}

In order to try to achieve further reduction in PNM rates of diabetic women, focus should be put on the various components constituting overall perinatal outcome in the different stages of the diabetic pregnancy. A closer examination of the various components comprising PNM rate may help elucidate specific points at which intervention might assist in the overall reduction of PNM in the diabetic population.

Numerous studies have demonstrated that there is an inverse relationship between maternal blood glucose levels and adverse pregnancy outcome. Pioneer works done during the 1960s and 1970s allowed to plot the inverse relationship between mean blood glucose (MBG) levels and PNM. These studies suggest that normalization of blood glucose levels might equal the PNM in the diabetic population to that of the nondiabetic population.⁴⁰ Karlsson and Kjellmer divided their diabetic gravid patients into three groups according to White's classification and MBG levels. MBG levels <100, 100–150, and >150 were related to PNM of 3.8%, 16%, and 24% respectively, but no association was found between White's classification and PNM.⁴⁰ The established inverse relationship between maternal metabolic control in

patients with pregestational diabetes and the risk for PNM⁴¹ was also demonstrated in patients with gestational diabetes (also related to maternal age and obesity).^{42,43} Population-based studies showed that for women with PGDM, 16%–28% of PNM is due to congenital malformations, and an additional 21%–41% is due to preterm delivery.^{39,44} Since the rates of both complications improve with prepregnancy care,⁴⁵ it is not surprising that Wahabi et al.⁴⁶ found in their meta-analysis that the PNM rate in women, who attended prepregnancy care programs, was reduced by 66% compared to those who did not.⁴⁶

Tables 59.2 and 59.3 summarize data regarding PNM and its various components in women with pregestational and gestational diabetes, respectively.

Early pregnancy loss

The altered intrauterine conditions in women with diabetes are probably associated with increase in early pregnancy loss rate. However, the exact quantification of the added risk in the diabetic population is difficult to assess due to the indefinable incidence of miscarriages in the general population.^{53,54}

Pregestational diabetes

The incidence of pregnancy loss in the diabetic population has declined substantially since the introduction of insulin in the early twentieth century. During the 1940s and 1950s, the reported pregnancy loss rate (“sudden fetal death”) was approximately 20%.⁵⁵ This might reflect the association between enhanced glycemic control (both preconception and during the first weeks of organogenesis) and the decreased rate of malformations.⁵⁶ Most of the studied reporting outcome of miscarriage included patients with pregestational diabetes, without a specific distinction between type 1 and type 2 diabetes. The reported rate of spontaneous abortions in women with Type 1 diabetes is approximately 17%.⁵⁷ The pooled estimate risk for early pregnancy loss in patients with type 1 and type 2 diabetes was calculated to be 3.23 RR (95% CI 1.64–6.36).³

Good glycemic control around the period of conception reduces the risk of early pregnancy loss to that observed in the nondiabetic population. High levels of HbA1c above normal range showed progressively high pregnancy loss rates. Lower levels of HbA1c were associated with lower early pregnancy loss rates among women with Type 1 diabetes mellitus (DM).^{22,58,59} Therefore, HbA1c can be regarded as an indirect measure of adverse outcome and be used for quality control.

A threshold level of HbA1c of 10%–12% correlating with MBG of 150–170 mg/dL is suggested as the upper limit for reducing the risk of spontaneous abortions.⁶⁰

Gestational diabetes mellitus

Only few studies investigating gestational diabetes mellitus (GDM) and pregnancy outcome have included *early* pregnancy loss as one of the outcome measures examined. Therefore, there is a scarcity of data concerning the exact

proportion of spontaneous pregnancy loss in this specific subgroup of diabetic patients.

Rudge et al.⁶¹ described pregnancy results in women with abnormal glucose tolerance including women diagnosed with GDM. They reported an abortion rate of 0.8% in the group of patients with altered diurnal glycemic profile without frank diabetes (as opposed to no abortions in the control group). There is evidence to support the theory that some metabolic abnormalities such as insulin resistance and high levels of fasting blood glucose may be apparent at early stages of pregnancy in women who are subsequently diagnosed with gestational diabetes.⁶² An alternative explanation is that this constitutes a group of women with undiagnosed Type 2 diabetes.

These studies and others offer circumferential support that GDM represents a metabolic disorder that interferes with the outcome of pregnancy from conception to delivery even though it is generally diagnosed throughout the third trimester.

Stillbirth (late fetal loss)

Stillbirth is a major component of PNM in the diabetic population (see Tables 59.2 and 59.3).

Congenital malformations are thought to be the most established causes of stillbirth in the diabetic population. The most common malformations are cardiovascular and neural tube defects,² but diabetes was not found to be predictive of any specific malformations.^{24,63,64}

Fetal metabolic acidosis with and without hypoxemia (as discussed earlier) is more prevalent in the diabetic population.^{36,37,65} Their presence may offer an additional explanation for late fetal demise in the diabetic population. Most studies investigating the pathophysiological basis for fetal death unrelated to congenital anomalies were done in women with PGDM,^{34,65} but it is reasonable to assume that women with GDM may share the same pathophysiological events as they also present the same high stillbirth rates.

The higher prevalence of other recognized risk factors for stillbirth such as maternal obesity, hypertension, and advanced maternal age in the diabetic population may all contribute to higher stillbirth rates.^{2,66} Late fetal death occurs more often in women with poor metabolic control, ketoacidosis, and vascular complications probably as a result of fetal metabolic acidemia and hypoxemia.⁶⁷ Landon et al.⁶⁷ found that women with Type 1 diabetes with vascular complications were at greater risk for abnormal fetal surveillance tests and subjected to more obstetric interventions such as induction of labor. In the group of patients who needed intervention, fetal cord pH was significantly lower than the nonintervention group. This may also serve as an indirect measure of fetal acidemia (in diabetic women as a possible cause of fetal compromise that may lead to intrauterine fetal death).

Pregestational diabetes

The reported rate of *congenital malformation* in patients with Type 1 diabetes in some population-based studies is

Table 59.2 PNM in PGDM

Author	#	Total PNM	Stillbirth	Neonatal death	Preterm	Macrosomia LGA	Birth trauma	Congenital anomalies
CEMACH ²	3808 (2767 Type 1; 1041 Type 2)	NA	26.8/1000 (Type 1 25.8/1000; Type 2 29.2/1000)	9.3/1000 (Type 1 9.3/1000; Type 2 9.2/1000)	36%	Macrosomia 21% ^a ; LGA 51.7%	Shoulder dystocia 7.9%; Erb's palsy 4.5/1000	41.8/1000
French multicentric ¹⁷	435 (289 Type 1; 146 Type 2)	44/1000	34.5/1000	Type 1 3/1000; Type 2 21/1000	38.2%	Macrosomia 17.3%	Shoulder dystocia 7.6%	41/1000
Machintosh et al. ¹⁶	2359 (1707 Type 1; 652 Type 2)	31.8/1000	26.8/1000	9.3/1000	NA	NA	NA	46/1000
Jensen et al. ³⁹	1215 (Type 1)	31/1000	21/1000	NA	41.7%	LGA 62.5%	NA	50/1000
Clausen and Matheisen ⁴⁷	301 (240 Type 1; 61 Type 2)	66/1000 (Type 2)	NA	NA	38% Type 1 31% Type 2	LGA 51% Type 1; 56% Type 2 Macrosomia 5% Type 1; 8% Type 2	NA	29/1000 (Type 1) 67/1000 (Type 2)
Evers et al. ¹⁵	323 Type 1	28/1000	18.5/1000	9.25/1000	32.2%	LGA 45.1%	Shoulder dystocia 14%	88/1000
ATLANTIC-DIP ¹¹	104(80 Type 1, 24 Type 2)	25/1000	25/1000	NA	12%	32%	NA	24/1000
Tennant et al. ⁴⁸	1548 (1206 Type 1, 342 Type 2)	NA	26.5/1000	4/1000	NA	NA	NA	NA

^a No significant difference in macrosomia rate between type 1 and type 2.

Table 59.3 Perinatal mortality in gestational diabetes mellitus

Author	#	Total PNM	Stillbirth	Neonatal death	Preterm	Macrosomia LGA	Birth trauma	Metabolic
Crowther et al. ⁴⁹	1000 (490 intervention, 510 routine care)	NA	0/506 vs. 3/524	0/506 vs. 2/524	NA	Macrosomia 10% vs. 21% LGA 13% vs. 22%	Shoulder dystocia 1% vs. 3% RR 0.46 (95% CI 0.19–1.10)	Jaundice 9% (both)
O'sullivan et al. ⁴²	187 GDM	64/1000	NA	NA	22.5%	NA	NA	NA
Dunne et al. ⁵⁰	216 ^a	NA	0	0	NA	LGA 25%–37%	NA	NA
Ramtoola et al. ⁵¹	294	116/1000	81/1000	38/1000	22%	Macrosomia 16%	NA	Hypoglycemia 14% Hyperbilirubinemia 39%
Ray et al. ¹⁴	428	NA	NA	NA	19.2%	LGA 15.9%	Shoulder dystocia 3%	NA
Tundidor et al. ⁵²	2299	5/1000	NA	NA	5.7%	LGA 10.4%	2.2%	Jaundice 3.5% Hypocalcemia 1.5%

^a GDM + IGT.

three- to fivefold higher than that of the general population.^{19,57} Congenital anomalies in women with Type 2 diabetes are also significantly higher than that of the general population and contribute to the increased PNM rate reported in this subgroup of patients.^{16,17} The congenital malformation rate in patients with Type 2 diabetes is equal to or even exceeds that of Type 1 diabetes.^{16,17,68} A meta-analysis that included an overall number of 3088 women with PGDM, conducted by Wahabi et al.,⁴⁶ found that pre-pregnancy care (glycemic control being the most important aspect) reduced the rate of congenital malformations from 7.4% to 1.9%, a rate similar to that reported for the background population.⁴⁶

Stillbirth rate in women with pregestational diabetes may reach 28–46/1000 live births—a rate three to five times higher than that of the general population.^{2,16,43,48} Lauenborg et al.,²⁴ in an audit on 25 cases of stillbirth in Type 1 diabetes patients, found a direct relationship between poor glycemic control both before and during pregnancy (measured by HbA1c levels) and a higher incidence of stillbirth. The relative risk for stillbirth in patients with Type 2 diabetes was found to be 4.7 (95% CI 3.7–6.0).¹⁶ Cundy et al.⁴³ reported a sevenfold increase in the risk for late fetal death in women with Type 2 diabetes that contributed to a high PNM rate of 46/1000 in that study. This was attributed to maternal factors such as obesity and advanced maternal age more prevalent in his study group. Furthermore, patients with Type 2 diabetes tend to be of lower socioeconomic class and part of an ethnic minority group, demographic differences that are interrelated to lack of preconception care (PCC) and may be confounding in the interpretation of results.^{2,16,43}

Tennant et al.⁴⁸ found that increasing periconception HbA1c concentration (for values above 49 mmol/mol), history of retinopathy, and lack of prepregnancy folic acid consumption were all associated with increased odds of fetal and infant death. There was no difference in the risk of fetal and/or infant death in women with Type 1 diabetes compared with those with Type 2, nor was there any evidence that the associations with HbA1c concentration, folic acid consumption, or history of retinopathy were different between types. Damm et al.⁶⁹ defined a composite endpoint of poor outcome in late pregnancy that included preterm delivery, preeclampsia, both preterm delivery and preeclampsia, stillbirth, and death within 1 week postnatally in women with Type 1 PGDM. They found that elevated HbA1c, high glucose spikes, and out-of-range plasma glucose levels in the third trimester, and albuminuria in early pregnancy, are associated with poor late-pregnancy outcomes.

Gestational diabetes mellitus

The stillbirth rate in patients with GDM is greater than that of the general population. The exact extent of increase in stillbirth rates is dependent upon the severity of glucose intolerance and degree of glycemic control. Stillbirth rates are only slightly increased when good glycemic control is achieved (stillbirth rate of 4.8 vs. 4.2 per 1000).¹⁵ Pettitt et al.⁶⁶ reported an increased risk of stillbirth mainly related to excessive fetal growth, which is also a measure of increased hyperglycemia

and hyperinsulinemia. The threshold for this pregnancy complication seems to be between 105 and 110 MBG; patients who achieve glycemic control below these values have a stillbirth rate comparable to those of the general population.⁶⁰

Neonatal death

Preterm delivery

Pregestational diabetes Preterm delivery is strongly related to adverse neonatal outcome.^{2,4,17} Over one-third of infants of pregestational diabetic mothers were born prematurely.² The rate of preterm delivery (both spontaneous and induced) in the Type 1 diabetic population is as high as 45%.¹⁷ Poor glycemic control (elevated HbA1c levels) and vascular complications (preeclampsia and nephropathy) are predictive factors for preterm labor.^{70–72}

The CEMACH enquiry reported the risk for preterm delivery in the diabetic population (type 1 and type 2 diabetes) to be nearly fivefold higher in comparison to the general population. Up to two-thirds of preterm deliveries were induced (“medically indicated”), and nearly 37% of them were due to presumed fetal compromise.² Some studies indicate that the proportion of induced preterm delivery due to presumed fetal compromise is greater in the diabetic population than that of the general population.²

Diabetes complicated by nephropathy or vascular disease causes an overall higher preterm delivery rate even when compared to a group of women with chronic hypertension, which might suggest there are other pathophysiological factors contributing to the adverse outcome.⁷⁰

Gestational diabetes mellitus There is an association between increased incidence of preterm delivery and gestational diabetes. Hedderson et al.⁷³ found that the risk for preterm delivery increased with increasing levels of glycemia (ranging from abnormal screening, but normal diagnostic glucose tolerance test to GDM). The relative risk for preterm labor was 1.42 (95% CI [1.15–1.77]) for the GDM group compared to normal controls. This association was also present for both induced and spontaneous preterm labor.^{73–75}

The degree of glucose intolerance or “early onset” of GDM is linked to a higher incidence of preterm labor. This may suggest an inverse relation between length of pregnancy and poor glycemic control and identify poor glycemic control as a marker of increased risk for preterm delivery.¹³

Macrosomia

Pregestational diabetes Macrosomia is associated with increased PNM and increased birth trauma. Birth-related trauma in women with pregestational diabetes is much higher than those in the general population: shoulder dystocia (more than twofold), birth-related fractures, and Erb’s palsy (more than tenfold).^{2,14,62} Higher rates of shoulder dystocia carry an increased risk of PNM. Sheiner et al. found PNM rates of 3.7% in infants suffering from shoulder dystocia vs. 0.5% in those without (OR 7.4 95% C.I [3.5–14.9]).⁷⁶

Mondestin et al. reported that PNM is increased among diabetic pregnancies at all birth weight categories over 1250 g,⁷⁷ but especially when fetal weight exceeded 4000 g, thus doubling the risk of fetal death in the diabetic population reaching 5.9/1000 births (adjusted R.R 2, 95% CI 1.8–2.2).⁷⁷

There was no significant difference between the rates of macrosomia in infants born to women with Type 1 diabetes compared with those born to women with Type 2 diabetes.² In unselected diabetic populations of patients with type 1 and type 2 diabetes, up to 50% of infants of diabetic mothers are born at weights >90th percentile. These patients were suboptimal in their glycemic control, as reflected by HbA1c levels.^{2,62,76} The risk for delivery of a macrosomic child is directly related to glycemic control measures throughout pregnancy.

Gestational diabetes mellitus High rate of macrosomia is also reported in infants of mothers diagnosed with GDM (increased risk of two- to fourfold).^{5,13} Women with GDM who attend an intensive pregnancy surveillance have a fourfold decrease in the risk of birth-related complications compared with GDM patients receiving “standard” prenatal care.⁴⁹

Langer et al.⁷⁸ demonstrated the relationship between glycemic control (namely, MBG levels <105) and reduced incidence of macrosomia.

The aforementioned text is not direct evidence for the relationship between metabolic control, macrosomia, and reduced PNM. However, it is logical to assume that intensive prenatal care results in better glycemic control that contributes to improved outcome.

Yee et al.⁷⁹ found that in overweight and obese women diagnosed with GDM, third trimester weight loss was associated with a decreased risk of macrosomia, as well as a decreased rate of cesarean delivery and NICU admission.

Respiratory and metabolic complications

Admission to neonatal intensive care units (NICUs) or other special care units is more common in infants of diabetic mothers and reaches up to 50% of neonates.^{2,17,38}

The NICU admission rate is an indirect measure of morbidity and of quality of care in the diabetic population (both PGDM and GDM). The majority of admissions are due to a myriad of conditions that may all contribute to early or late PNM in the diabetic population, such as hypoglycemia, hyperbilirubinemia, and respiratory distress due to lung immaturity. Premature infants are more prone to episodes of hypoglycemia than term infants³⁸; however, even after correction for preterm birth, the proportion of infants of diabetic mothers hospitalized in NICU is still significantly higher than the general population.^{2,38,72,74} For instance, the rate of hypoglycemia in infants born to Type 1 diabetes may reach 50% in premature infants and 23% in term infants.⁷¹ Pulmonary complications ranging from transient tachypnea to respiratory distress are more common in infants of diabetic mothers resulting from abnormal lung maturation

caused by hyperinsulinemia.⁶⁰ There is a direct relationship between higher rates of respiratory complications and poor glycemic control,^{29,38} but there is little information concerning the estimated threshold of glycemia that carries an increased risk for respiratory complications.⁶⁰ Another problem is the lack of data relating directly to the relationship between higher rates of these “metabolic” complication and PNM. These complications may carry an increased risk for morbidity and mortality, but the exact quantification of this added risk is difficult due to lack of information. Dani et al.⁸⁰ demonstrated that infants of GDMs had lower levels of glucose and higher levels of pyruvate, histidine, alanine, valine, methionine, arginine, lysine, hypoxanthine, lipoprotein, and lipid than controls, but did not find any clinical differences in outcomes.⁸⁰

It is believed that with modern resources, the greater part of these complications have a minor influence on actual mortality rates but may cause increase in morbidity.

What can be done to reduce the rate of PNM in pregnancies complicated by diabetes?

The St. Vincent Declaration given at 1989 set as a goal to equalize pregnancy outcomes of women with diabetes mellitus to those of nondiabetic women within 5 years. Although there has been considerable advancement in the ability to detect fetal anomalies and establish fetal well-being and maturity, this goal, which was perceived as feasible at the time (especially in light of the conceivable improvement in pregnancy outcomes of insulin-dependent diabetic women), has not been met. The presence of diabetes is thought to increase the risk for congenital malformation by as much as 10-fold, stillbirth up to 5-fold, and neonatal death 3–4-fold.³

Furthermore, some reports imply that the trend toward decline in PNM rates in the diabetic population is less than the decline in PNM observed in the general population during the same time period.^{4,22}

Colstrup et al.⁸¹ sought to evaluate whether the goals of the 1989 St. Vincent Declaration have been obtained concerning fetal and neonatal complications. Their study included 12 population-based studies published between 2003 and 2013, with a total of 14,099 women with T1DM. The authors found that the risk of adverse pregnancy outcomes (including congenital anomalies, preterm deliveries, and macrosomia) was two to five times increased in women with T1DM compared with the general population. They concluded that the goals of the St. Vincent Declaration have not been achieved.

Good glycemic control is a fundamental part in avoiding adverse pregnancy outcome. In order to elucidate possible causes for this apparent failure to meet goals set at St. Vincent, two important issues must be addressed. The first issue is the extent at which the diabetic population meets the healthcare practitioners’ criteria for “good diabetic control.”

There are very few randomized control trials (RCTs) regarding the relationship between glycemic control and pregnancy outcome.⁸² The Diabetes Control and Complications Trial (DCCT) suggested that early and tight glycemic control might reduce pregnancy loss rates and congenital anomaly rates equal to those of the general population.⁸³ This finding was not repeated in Cochrane's review on three other RCTs.⁸² Conversely, observational studies (which included less selective populations) failed to demonstrate such a substantial reduction.^{2,17} Some of the difference can be explained by the fact that different cutoff points for HbA1c levels to distinguish between poor and good glycemic control were used. There were also dissimilarities regarding the time in which the predictive HbA1c measurement was taken (first trimester, first antenatal visit, etc.) and the number of measurements used to categorize women in "poor" vs. "optimal" control. It is clear that a single HbA1c measurement cannot be used as an absolute predictor for pregnancy complications. HbA1c may reflect long-term average glycemic control, but there are many limitations to its use, raising important questions regarding its adequacy as a measure of glycemic control (vs. other methods such as self-monitoring blood glucose levels, MBG, or fasting blood glucose). Furthermore, the optimal HbA1c level that should be set as a treatment goal is beyond the scope of this chapter. Langer et al.⁸⁴ provided support for those calling to rely on maternal glucose levels as a measure of glycemic control rather than HbA1c. They showed that strict glycemic control resulting in near normoglycemia leads to perinatal morbidity and mortality rates almost comparable to those of the nondiabetic

population. Other studies also hold up the hypothesis that intensive care consisting of maternal glucose monitoring and decisions concerning insulin treatment based upon its results are related with enhanced perinatal outcome.^{85,86}

The second issue regarding the failure to meet St. Vincent goals is related to preconception counseling in the diabetic population. Preconception counseling is significant due to the fact that the crucial phase of organogenesis takes part during early pregnancy, at which timely and adequate metabolic control is important for optimal pregnancy outcome.

A meta-analysis¹² reviewing 14 cohort studies concerning patients with PGDM, calculated a major malformation rate of 2.1% in women attending PCC vs. 3.5% in those without PCC (RR 0.36, 95% CI 0.22–0.59). This connection between PCC and reduction in adverse pregnancy outcome (mainly spontaneous abortions and congenital anomalies) was also demonstrated in other studies.^{17,19,39,87} The topic of PCC may need special attention in women with Type 2 DM as they tend to differ in lifestyle, age, and economical background and often require change in treatment regime (oral antidiabetic drugs or insulin).^{2,19,47}

The route toward improved PCC attendance remains somewhat obscure. Some of the factors associated with low attendance rates such as education level, socioeconomic status, and ethnic background are not in the hands of healthcare providers. However, diabetic patients should be counseled against PCC failure and unplanned pregnancies and provided with accessible preconception education and care programs.

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60 Short-term implications of gestational diabetes mellitus: The neonate

Delphine Mitanchez, Catherine Yzydorczyk, and Umberto Simeoni

Diabetes mellitus during pregnancy is responsible for significant complications in the fetus and neonate. Risk is higher in pregestational diabetes, but also if pure gestational diabetes (GDM) is not recognized and well managed. The current worldwide pandemic of type 2 diabetes (T2D) has devastating effects with T2D representing up to 25% of pregnancies with pregestational diabetes.¹ The rate of fetal and neonatal complications in these pregnancies is not different to those affected by type 1 diabetes (T1D). Diabetes in pregnancy is still responsible for a significant perinatal mortality and morbidity in many countries.²

Optimizing diabetic care before and during pregnancy reduces the risk of neonatal complications. Indeed, thanks to considerable advances in the management of diabetes in pregnancy, whether preexisting (type 1 or type 2) or purely gestational, many infants born to diabetic mothers experience a healthy neonatal course, especially in high-income countries. Treatment of GDM has been shown to reduce specific or composite neonatal outcomes.³ However, implementation of strategies to limit the consequences of diabetes in pregnancy to the offspring is still difficult to achieve in many countries, particularly in low-income and developing ones. While even in countries that enjoy high standards of perinatal care, GDM can be misdiagnosed and neonatal complications can occur that need a specific pediatric management.

Pathophysiology of fetal and neonatal complications

Poorly controlled maternal pregestational diabetes significantly increases the risk of offspring malformations. Maternal hyperglycemia results in glucose metabolism in the developing embryo that alters various molecular chain reactions: (1) altered cell lipid metabolism (newborn infants born to diabetic mothers have a lower status of arachidonic acid concentrations,⁴ therefore altering the production

of prostaglandins,⁵ particularly prostaglandin E2 that is involved in maintaining the patency of the ductus arteriosus in utero)⁶; (2) high glucose levels induce an excessive production of reactive oxygen species that has been shown to cause oxidative stress and subsequently increase the risk of fetal malformations, notably neural tube defect⁷; and also (3) high glucose induces the activation of the cascades of proteins involved in apoptotic cell death, including the caspase families. Notably, it has been shown that hyperglycemia upregulates caspase-8 activity (enhanced cleavage) and may be involved in hyperglycemia-associated.⁸ Despite a growing understanding of the molecular basis of diabetic embryopathy, mechanisms are not yet fully understood.⁹

Likewise, the mechanisms of the impact of maternal diabetes on fetal and neonatal physiology need further research. Pedersen's hypothesis, formulated more than 50 years ago, suggested that fetal overgrowth was related to increased transplacental transfer of maternal glucose, thus stimulating the release of insulin by the fetal beta cells and inducing subsequent macrosomia.¹⁰ More recently, studies have characterized the link between maternal glycemia and neonatal macrosomia or fat mass.¹¹ Fetal hyperinsulinism not only affects fetal growth but is also currently considered as the central factor in the pathophysiology cascade summarized in Figure 60.1.

Furthermore, despite tight glycemic control, macrosomia still persists in some cases. This suggests that mechanisms other than those evoked by Pedersen contribute to fetal overgrowth. Evidence has recently emerged on the involvement of the maternal metabolic environment and of placental modifications in fetal overgrowth. In GDM, the maternal metabolic environment is characterized by insulin resistance (IR) and inflammation.¹² Both conditions influence fetal growth. IR facilitates maternal hypertriglyceridemia, which in turn enhances substrate availability to the fetus. Furthermore, specific alterations of the placental transcriptome have been evidenced in the context of the altered environment of diabetic pregnancy. For example, genes for lipid

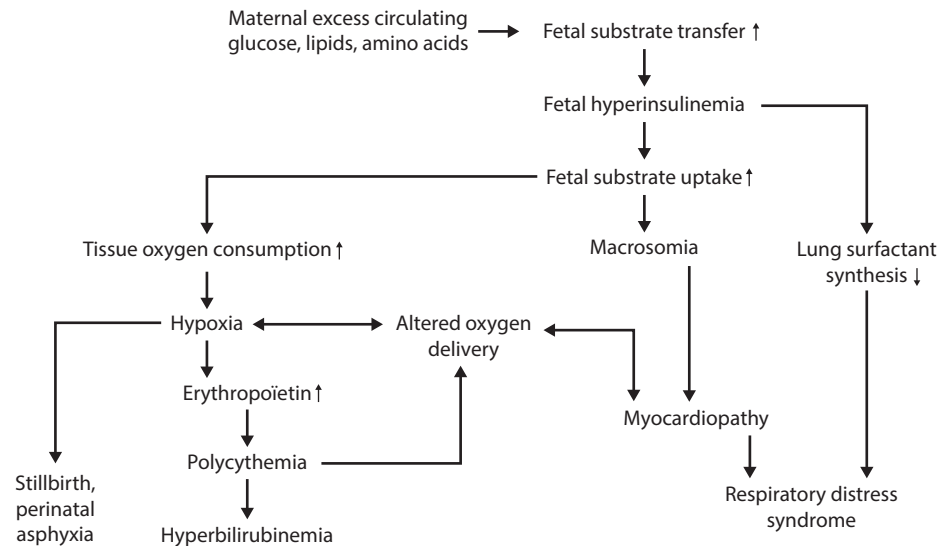


Figure 60.1 Intrauterine exposure to maternal diabetes and short-term outcomes.

transport have been shown to be upregulated in the placenta of women with GDM, as well as are genes for inflammatory pathways.¹³ Altogether, such alterations directly or indirectly alter the availability of the substrates to the fetus either by increasing their source or by modifying the maternal–fetal interface.

In addition, altered vascular structure and function, altered microcirculation, placental immaturity, and poor tissue oxygenation are important determinants of both short- and long-term outcomes.

Fetal malformations

Birth defects remain one of the leading causes of infant mortality. It is estimated that 8 million infants in the world (185,000 in the United States) are born each year with major malformations. Many of these birth defects can be attributed to pregestational diabetes.⁹

Major congenital malformations reported in babies of pregestational diabetic mothers are heart malformations (transposition of great vessels, ventricular or atrial septal defects, coarctation of the aorta), caudal regression syndrome, central nervous system defects (NTD, including anencephaly), gut malformations (duodenal and anorectal atresia, hypoplastic left colon), and skeletal and genital–urinary tract anomalies.¹⁴

Poor maternal glycemic control in the periconceptual period increases the risk of malformations. The rates of fetal malformations appear to be similar in maternal T1D and T2D.¹⁵ The risk for congenital malformations in preexisting diabetes is 1.9- to 10-fold higher than in the total population.¹⁶ The risk is slightly increased in the case of GDM compared to the general population (ORs between 1.1 and 1.3) but is much lower than in women with pregestational diabetes.¹⁶ The malformations described are similar to those reported in pregestational diabetes, especially cardiovascular defects and anomalies involving the musculoskeletal and central nervous systems.^{17,18}

A relationship has been established between the risk of malformations in GDM and maternal blood glucose level.¹⁸ Such risk also increases with maternal body mass index (BMI) and when GDM is diagnosed during early pregnancy. These observations suggest that the increased risk could be related to the inclusion of women with undiagnosed T2D in the GDM groups.¹⁹

Perinatal death and asphyxia

Both types of pregestational diabetes are associated with an increased risk of stillbirth. In T1D, a three- to fivefold risk increase has been found in various countries.²⁰ In T2D, the risk of perinatal death is even higher than in T1D (OR = 1.5 [1.15–1.96]).²¹ Pregnancies in women who have newly diagnosed T2D have significantly worse outcomes, probably related to obesity, hypertension, and maternal age. In T2D, the BMI of women with a stillbirth has been shown to be higher (+2 kg/m²) than in women with live-born infants, suggesting that obesity can strongly contribute to perinatal death in women with T2D.²² Unlike in pregestational diabetes, the increased rate of fetal deaths in the second and third trimesters of pregnancy is debatable in cases of GDM. Although it is difficult to demonstrate a consistent increase in GDM, the risk for stillbirth appears slightly increased but is lower than in T1D and T2D.²⁰ Cundy et al. showed that, after exclusion of newly diagnosed T2D in the GDM group, perinatal mortality was similar to that in the general population.²² According to these data, the increased risk of perinatal death in cases of GDM, reported in some studies, may be attributable to undiagnosed T2D.

Only 50% of stillbirths (fetal death after 20–22 gestational weeks [GW]) can be explained by causes such as intrauterine growth restriction, preeclampsia, acute asphyxia, intrauterine infection, or congenital malformation. But in the remaining 50%, the pathophysiology is likely to be multifactorial and may result from chronic fetal asphyxia and fetal

cardiac dysfunction. In T1D offspring, more than 75% of perinatal deaths are attributed to congenital anomalies or complications of preterm birth, whereas in T2D offspring, the deaths are mainly due to stillbirth, chorioamnionitis, or birth asphyxia.²²

The rate of neonatal deaths, even in high-income countries, is still around 3% in T1D or in T2D and is much lower, close to the rates of nondiabetic pregnancies in the case of pure GDM. Strict glycemic control may reduce the number of stillbirths in women with T1D and T2D.²³

Increased risk of perinatal asphyxia has been reported in diabetic pregnancies in a number of studies. Different risk factors have been identified in T1D: nephropathy developing during pregnancy, hyperglycemia 6 hours before delivery, preterm birth, and lower gestational age.²⁴ In cases of GDM, the incidence of perinatal asphyxia is not increased, nor is it influenced by maternal treatment.^{25,26} Macrosomic infants (>4500 g) are at increased risk of asphyxia-linked morbidities whatever is the cause of macrosomia.²⁷

Preterm birth

A number of studies have reported an increased risk of preterm birth in case of maternal diabetes. However, it is difficult to determine the respective parts of spontaneous preterm delivery and of induced labor or cesarean section, because of frequent interventionistic approaches. The benefits of early delivery to avoid fetal death or shoulder dystocia must be balanced against the morbidity linked to preterm birth, particularly respiratory morbidity.

In pregestational diabetes, the rate of premature birth is increased up to 25%, with most of these being late preterm birth (34–36 GW).²⁸ In T1D, pregestational hypertension is related to preterm birth, whereas in T2D, third trimester glycosylated hemoglobin (HbA1c) is a predictor of prematurity.²⁹ GDM and glucose intolerance are risk factors for spontaneous preterm birth independently on other complications,³⁰ mean maternal glucose level was also related to the risk of preterm birth.^{31,32}

Fetal growth

Macrosomia

The concept of excessive fetal growth has been expressed either by the word “macrosomia” or by the expression “large for gestational age” (LGA). Macrosomia is usually defined by an upper birth weight threshold somewhere between 4,000 and 4,500 g, depending on the study. However, in this definition, gestational age is not taken into account. The term LGA corresponds to a birth weight ≥ 90 th percentile or $> +2SD$ (>97 th percentile) for gestational age. This more precise definition takes into consideration gestational age at birth and allows preterm newborns with excessive fetal growth to be identified.

Macrosomia observed in the case of newborns of diabetic mothers can be differentiated from other forms of

macrosomia as it is characterized by an excess body fat, an increased in muscle mass, and organomegaly without increased brain size and is thus asymmetric. There is a linear and continuous relationship between percentage body fat in newborns, maternal glycemia, and fetal insulin levels.³³

Hence, maternal diabetes during pregnancy, whatever its type, is a risk factor for macrosomia. Treatment of GDM significantly reduces the rate of macrosomia.^{3,34} In case of T1D, optimal glycemic control during pregnancy (i.e., HbA1c $\leq 7.0\%$) does not preclude a high incidence of fetal macrosomia. Some studies have found that third trimester HbA1c is an independent risk indicator for macrosomia, but it has a weak predictive capacity. HbA1c does not reflect intermittent hyperglycemia, mainly postprandial hyperglycemic episodes, that may be involved in accelerated fetal growth.^{35,36} The frequency of macrosomia or LGA is not different in T2D with respect to T1D,³⁷ even if in T2D, HbA1c is lower at booking and throughout gestation.²¹

Macrosomia, regardless of the cause, is in itself a risk factor for adverse perinatal outcomes, such as asphyxia and perinatal death, birth injury, respiratory distress, and hypoglycemia.^{27,38} Such risks increase as the birth weight or the birth percentile rise. An important complication of macrosomia is shoulder dystocia and subsequent birth injuries. Such risk is the highest for infants with a birth weight 4,500–4,999 g and $>5,000$ g, (ORs 2.4 [2.2–2.5] and 3.5 [3.0–4.2], respectively).²⁷ Among infants with Erb’s palsy in the general population in the British Isles, 53% were LGA.³⁹ Erb’s palsy is tenfold higher in case of pregestational diabetes.⁴⁰

Fetal growth restriction

Fetal growth restriction is less often associated with maternal diabetes but has been reported in association with severe vascular complications of advanced diabetes and poor placental perfusion.⁴¹ An interaction between preconceptional HbA1c and reduced weight at birth has been found.⁴² The hypothesis is that high glucose levels in early pregnancy harm placental development, especially when it is associated with microvascular disease. Placental growth is reduced and placental functions are impaired, resulting in fetal growth restriction. This situation exposed to the risk of preterm birth.

Other neonatal complications

Hypertrophic cardiomyopathy

Fetuses exposed to maternal hyperglycemia and hyperinsulinism are prone to develop hypertrophic cardiomyopathy. It primarily affects the interventricular septum but can extend to the myocardium in more severe cases. Contrary to what is described for macrosomia, the precise role of fetal growth factors and the influence of hyperglycemia on cardiomyocyte growth and function are poorly understood.⁴³

Myocardial hypertrophy is most often asymptomatic. It can sometimes lead to severe morbidity and mortality,

according to the severity and the extension of cardiac hypertrophy, especially in the case of obstructive septal hypertrophy.

Myocardial hypertrophy has been reported in both pregestational diabetes and GDM with a wide range of frequencies (between 25% and 75% of infants born to diabetic mothers).^{44,45} The incidence was lower in case of GDM comparing to pregestational diabetes.⁴⁶ The most recent studies showed that optimal maternal glycemic control does not entirely preclude interventricular septum hypertrophy and minor fetal cardiac function impairment, whatever is the type of diabetes.^{47,48}

Antenatal ultrasounds play an important role in monitoring fetal cardiac anatomy and function. Babies of women with diabetes should have an echocardiogram in the presence of clinical signs associated with congenital heart malformations or cardiomyopathy.

It is usually considered that heart hypertrophy resolves anatomically within few months. However, the long-term effect of diabetic cardiomyopathy on heart function remains to be elucidated.

Respiratory disorders

Neonatal respiratory distress syndrome

Newborns to diabetic mothers have increased risk of neonatal respiratory distress syndrome (RDS), a major cause for admission into neonatal intensive care units.

The principal mechanism relies in altered lung surfactant synthesis due to fetal hyperinsulinism. Insulin has been shown to alter prenatal surfactant. Delayed appearance of phosphatidylglycerol in amniotic fluid after 34 GW has been found in women with poorly managed diabetes. This risk has been found to be higher between 36 and 37 GW⁴⁹ and in cases of pregestational diabetes.⁵⁰

As a consequence, late preterm birth associated with RDS is a particular characteristic of intrauterine exposure to diabetes. Late preterm infants are at greater risk of neonatal morbidities than term infants. This risk is higher in the presence of additional maternal morbidity, particularly prenatal maternal exposure to hypertensive disorders of pregnancy and diabetes.⁵¹ In neonates delivered after 34 weeks, GDM should be considered as an independent risk factor for severe neonatal respiratory disorder.⁵²

Macrosomia (birth weight $\geq$ 4000 g), associated or not with GDM, is a risk factor for neonatal respiratory distress.^{53,54}

Complementary studies are necessary to determine whether in the case of diabetic pregnancies, changes need to be introduced in recommendations on antenatal steroid therapy to accelerate fetal lung maturation.

Other respiratory disorders

Besides RDS, infants born to diabetic mothers are exposed to an increased risk of transient tachypnea of the newborn, particularly in the context of cesarean birth, due to delayed reabsorption of alveolar liquid at birth.⁵⁵

Diabetes, but also maternal BMI, is associated with a higher risk of persistent pulmonary hypertension (PPH). However, other independent risk factors like macrosomia and cesarean deliveries might be in the causal pathway between diabetes, overweight, and PPH.⁵⁶ Furthermore, increased risk for meconium aspiration has been reported after diabetic pregnancy, together with increased risk of perinatal asphyxia. However, such complication affects mainly pregnancies complicated by severe preexisting diabetes.⁵⁷

Neonatal glucose disorders; hypoglycemia

It has long been known that a correlation exists between macrosomia, increased cord C-peptide levels, and neonatal hypoglycemia. The data collected by the HAPO study confirmed such relationship: neonatal hypoglycemia was strongly associated with elevated cord serum C-peptide levels. Infants with excessive size at birth were more likely to develop hypoglycemia and hyperinsulinemia.⁵⁸

The exact incidence of hypoglycemia in cases of maternal diabetes is difficult to assess due to the variable definitions used for neonatal hypoglycemia in the different studies. Comparisons with the risk observed in healthy newborns are difficult also because of different monitoring of blood glucose at birth most of the studies. The infant of diabetic mother is at risk of transient hyperinsulinism, which prevents at birth the normal activation of metabolic pathways producing glucose and ketone bodies and causes increased glucose consumption by tissues. However, severe hypoglycemia with clinical signs is unusual nowadays, probably because of the improvement of prenatal maternal care.⁵⁹

Glucose monitoring

The pathological significance of low blood glucose levels immediately after birth, in the absence of specific symptoms, is still questioned. An immediate fall in blood glucose concentration is observed after birth, reaching a nadir between 1 and 2 hours in healthy term infants. From 2 to 3 hours of age, blood glucose then rises spontaneously, even in the absence of any nutritional intake, due to the activation of metabolic regulatory pathways. Therefore, measurement of blood glucose level at this stage is not indicated in asymptomatic infants since normal levels cannot be distinguished from abnormal levels during this period and the incidence of hypoglycemia is likely to be overestimated.⁶⁰ The first measurement in asymptomatic neonates is recommended before the second feed, at around 3–4 hours of age, which generally allows identifying infants who cannot manage adequate early glucose homeostasis.

Regulatory pathways involved in glucose homeostasis are activated within the first 24 hours of life. Thus, at-risk infants who have not suffered hypoglycemia during the first 24 hours (glucose values above 2 mmol/L), who have been fed normally, and who are clinically stable do not present a higher risk of subsequent hypoglycemia. Then, blood glucose monitoring may be discontinued.

There is currently no consensus on the indications for systematic glucose blood monitoring in asymptomatic infants born to diabetic mothers. It seems reasonable to consider that LGA or growth-restricted infants born to diabetic mother may benefit from a blood glucose concentration check at 3–6-hour intervals during the first day of life. On the other hand, normal-grown infants of mothers with diet-controlled GDM should not be monitored.

Prevention and treatment

Early and frequent breastfeeding remains the key to prevent hypoglycemia, whatever the birth weight of the infant, as far as he or she is able to feed autonomously. Therefore, infants of diabetic mothers should be kept beside their mother, in the absence of any significant complications requiring a transfer to a special care neonatal unit, which corresponds to the majority of the cases in high-income countries. Even in mildly or moderately symptomatic infants with low blood glucose levels, sustained breastfeeding or eventually formula supplements should be tried first, provided a satisfactory clinical response is obtained. For newborns without clinical signs, therapeutic intervention is required when two consecutive blood glucose levels are below 2.0 mmol/L.⁶¹ In the case the infant is unable to feed, an IV glucose supplementation (3–6 mg/kg/hour) should be provided at constant rate of infusion, in order to avoid rebound hypoglycemia.

In the presence of severe symptoms, such as marked hypotonia, coma, seizures, or blood glucose level <1 mmol/L, an IV bolus dose of glucose (150–200 mg/kg) should be administered urgently, followed by constant rate infusion. It is necessary to check that thereafter blood glucose concentrations stabilize within the normal range.⁴³

Neonatal hypocalcemia

Neonatal hypocalcemia has been reported following diabetes during pregnancy, with an incidence up to about 30% in poorly controlled diabetes.⁶² The mechanism is still unclear but seems to involve an abnormal calcium phosphorus metabolism during pregnancy with decreased calcemia and vitamin D concentrations especially during the third trimester. The severity of hypocalcemia is related to the degree of maternal diabetes control. Neonatal hypoparathyroidism has been reported and may be in part secondary to maternal magnesium loss.⁶² Furthermore, some studies have reported an association between GDM and low maternal vitamin D status, particularly with poor blood glucose control. Conversely, there is growing evidence that women who develop GDM are more likely to be vitamin D deficient.⁶³ Other factors like prematurity and perinatal asphyxia can contribute to low calcium levels. There is no indication to screen healthy babies for hypocalcemia and hypomagnesemia.

Neonatal polycythemia and hyperbilirubinemia

Relative fetal hypoxia, secondary to insulin-induced high glucose uptake and metabolic rate (Figure 60.1), causes increased erythropoietin secretion and, as a consequence,

increased fetal red cell production. The incidence and the severity of polycythemia are in relation with poor maternal glycemic control.

Normovolemic polycythemia seen in infants from diabetic mother can lead to hyperviscosity. Early symptoms are unspecific. Feeding problems, plethoric aspect, cyanosis, lethargy, hypotonia, respiratory distress, jitteriness and irritability, seizure (due to multiple cerebral infarcts), necrotizing enterocolitis, hyperbilirubinemia, and hypoglycemia have all been found associated. Hypoglycemia is aggravated in infants of diabetic mothers due to increased glucose consumption by the increased red cell mass. Renal thrombosis and other forms of thrombosis are also more frequent in infants of diabetic mothers.

Treatment is still controversial. In asymptomatic infants, no treatment is needed except to avoid hypoglycemia. Polycythemia associated with clinical signs should be treated by partial exchange transfusion as early as possible.

Hyperbilirubinemia has been traditionally described as a neonatal complication of maternal diabetes. It is not a serious complication if nontoxic levels are treated, which is usually the case. The potential danger is kernicterus, which is not classically reported in cases of diabetes. In the HAPO study, hyperbilirubinemia was weakly associated with maternal blood glucose levels.¹¹ Polycythemia could be one of the causes, but additional mechanisms, such as preterm birth and poor liver conjugation, are likely to be involved.

Impact of maternal obesity on neonatal complications of GDM

Maternal obesity is associated with worse perinatal outcomes even in glucose-tolerant women. Macrosomia is the main complication reported in overweight or obese women, independently of diabetes.^{64–67} It is well recognized that neonates born to obese women, even if normally glucose tolerant, have increased fat mass.⁶⁸ As in GDM, increased adiposity at birth is related to maternal IR with excess of glucose and lipid availability and to increase systemic inflammation.¹²

The risk of fetal and infant deaths are two- to threefold higher for women who are obese at the start of pregnancy, after excluding pregnancies affected by congenital anomalies or pregestational diabetes.⁶⁹ Maternal obesity is associated with an increased risk of a range of structural anomalies, with the higher risk for neural tube defects.^{70,71}

The risk of GDM increases with maternal BMI.⁷² The overall population-attributable fraction of GDM related to overweight was estimated at 46.2%.⁷³

The benefit effect of treatment of diabetes on neonatal outcomes is lower in obese women even if targeted levels of glycemic control are achieved. Furthermore, when GDM is untreated or poorly controlled, overweight and obese women have a higher risk of poor neonatal composite outcome, compared to normal weight GDM women.^{26,74}

The combination of GDM and obesity has a greater impact on pregnancy outcomes than either GDM or obesity alone. This cumulative risk was shown for macrosomia, newborn

percent body fat, and birth trauma.⁷⁵ It was also reported for a composite neonatal outcome (birth weight > 4000 g, birth trauma, shoulder dystocia, hypoglycemia, or jaundice).⁷⁶

Conclusions

Severe neonatal complications (birth defects, perinatal deaths, or asphyxia) are mainly due to pregestational diabetes. Such serious complications reported in studies on GDM are likely due to undiagnosed prepregnancy T2D. Maternal diabetes during pregnancy, regardless of the type, is a risk factor for macrosomia or excessive fetal growth.

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61 Long-term outcomes after gestational diabetes mellitus exposure in the offspring

Delphine Mitanchez, Catherine Yzydorczyk, and Umberto Simeoni

An extensive literature is available, tracking health outcomes at adulthood for the offspring of diabetic mothers. Many studies have found that offspring of diabetic mothers face an increased risk of developing impaired glucose tolerance, hypertension (HT), overweight and obesity, and dyslipidemia, as well as other noncommunicable diseases. Such outcomes may be partly linked to genetic and lifestyle exposure. But there is increasing evidence that fetal exposure to maternal diabetes is one of the multiple risk factors of chronic diseases and, in particular, the metabolic syndrome (MS) in adults.

Effect of maternal diabetes on the offspring long-term health and risk for disease

Glucose intolerance and type 2 diabetes, overweight and obesity

Extensive data on the consequences of exposure to diabetes in utero on childhood overweight and obesity and risk of type 2 diabetes (T2D) have been obtained from studies on Pima Indians, a population with an exceptionally high prevalence of obesity and T2D due to genetic reasons. The prevalence of T2D in offspring of Pima women has been shown to increase up to sixfold in those with diabetic or prediabetic mothers, while diabetes during childhood and adolescence occurred almost exclusively among the offspring of diabetic and prediabetic mothers.¹ Accordingly, the offspring born to mothers with pregestational T2D or gestational diabetes mellitus (GDM) are heavier at birth and at every age than those born to nondiabetic mothers. There is evidence that the higher frequency of diabetes and obesity in the offspring of diabetic Pima women is not only due to their genetic susceptibility to obesity and diabetes. Studies including sibling pairs in which one sibling was born before and the other was born after the onset of maternal diabetes have brought interesting data.²

The risk of diabetes was significantly higher in siblings born after the mother developed diabetes than in those born before the mother's diagnosis of diabetes (odds ratio 3.7, $P = 0.02$) and the mean of body mass index (BMI) was 2.6 kg/m² higher in offspring of diabetic than in offspring of nondiabetic pregnancies ($P = 0.003$).³ Furthermore, there were no significant differences in the risk of diabetes or in BMI between offspring according to the paternal diabetic status and onset of diabetes.

These results were confirmed in other ethnic groups. In a large prospective Swedish cohort study, BMI at 18 years old of men whose mothers had diabetes mellitus during their pregnancy was on average 0.94 kg/m² greater (95% [CI], 0.35–1.52) than in their siblings born before their mother was diagnosed with diabetes, after adjustment for maternal age, parity, and education.⁴ These findings suggest that intra-uterine exposure to maternal diabetes has a negative impact on health outcomes, beyond genetic and lifestyle factors. In a Nordic Caucasian population, the risk for T2D and prediabetes was found to be increased in offspring born to mothers with diet-treated GDM (7.76 [95% CI 2.6–23.4]) and mothers with type 1 diabetes (T1D) (4.0 [95% CI 1.3–11.9]).⁵ These results were confirmed by others.² Interestingly, adult offspring of women with T1D are more likely to have impaired glucose tolerance and a deficient insulin secretory response to glucose than the offspring of fathers with T1D.⁶ These data favor the effect of exposure to maternal diabetes during pregnancy on the risk of T2D, regardless of the type of maternal diabetes and beyond transmitted diabetic genes.

The longitudinal cohort Exploring Perinatal Outcome among Children (EPOCH) study found that youth exposed to maternal GDM had a higher average BMI growth trajectory from 27 months through 13 years of age and higher BMI growth velocity starting at age 10–13 years. But no differences were noted in growth velocity until 26 months of age.⁷ The effects of in utero exposure to diabetes thus extend beyond neonatal and early childhood periods and emerge during puberty, a sensitive period for the development of glucose intolerance and obesity.

Cardiovascular and renal diseases

Offspring of Pima mothers who had diabetes during pregnancy had higher systolic arterial blood pressure than offspring of mothers who did not develop T2D until after pregnancy: this was independent of the levels of adiposity.⁸ Adverse cardiovascular effects of maternal diabetes on offspring were observed early in life and in other ethnic groups. When compared with offspring not exposed to maternal diabetes, exposed offspring have a worse cardiovascular risk profile with the increased levels of circulating cellular adhesion molecules, which are biomarkers of adverse endothelium perturbation. These markers are related to the earliest preclinical stages of atherosclerosis and diabetes.⁹ Epidemiological studies that focused on blood pressure values in the adult offspring of mothers with GDM found a low increase in systolic blood pressure (SBP). A recent systematic review confirmed the association between exposure to maternal diabetes and SBP in childhood. But this association was only significant in male offspring. Furthermore, there is some evidence that this association may be influenced by maternal prepregnancy BMI.¹⁰

Endothelial dysfunction (ED) has been thought to be critical in the development of vascular disease, notably in HT.¹¹ ED can be characterized by a loss of regulatory functions related to vascular tone, inflammation, and oxidative stress but also by an impaired vasculogenesis and capacity of repair mediated by circulating endothelial progenitor cells (EPCs). These cells are now considered as a strong biomarker to assess ED and have been considered as endothelial colony-forming cells (ECFCs).¹² It was shown *in vitro* and *in vivo* that hyperglycemia or exposure of ECFCs to a diabetic intrauterine environment reduced ECFC colony formation and capillary-like tube formation¹³ and increased senescence and reduced proliferation.¹⁴ These data provide potential mechanistic insights into the development of ED and the long-term cardiovascular complications observed in newborns of diabetic pregnancies.

Exposure to a diabetic intrauterine environment is also considered as a strong risk factor for renal disease. Diabetic nephropathy is the major cause of end-stage renal disease.¹⁵ In Pima Indians, an increase in urinary albumin excretion (UAE) in offspring of diabetic mothers has been observed: UAE was 58% in offspring of mothers with GDM, 43% in offspring of mothers who develop diabetes after pregnancy, and 40% in offspring of nondiabetic mothers.¹⁶ These functional changes might result in damage to the developing glomeruli, possibly related to a similar process of decreased number of nephrons.

Limitations and confounding factors

Some limitations in the available studies must, however, be taken into consideration. Most studies encounter major difficulties to separate the responsibility of fetal exposure to maternal hyperglycemia alone in the long-term outcome, from fetal exposure to coexisting maternal manifestations like overweight/obesity. Different interrelated mechanisms play a role in the modification of fetal nutrition and metabolism and may have an impact on the long-term outcome.

In GDM, apart from hyperglycemia, the maternal metabolic environment is characterized by insulin resistance (IR) and inflammation.¹⁷ Both conditions influence fetal growth. IR facilitates maternal hypertriglyceridemia that enhances substrate availability to the fetus. Other mechanisms influence nutrient supply to the fetus. The placental transcriptome has been shown to be a target of the altered environment of diabetic pregnancy. For example, genes for lipids transport have been shown to be upregulated in the placenta of women with GDM, as well as are genes for inflammatory pathways.^{18,19} Altogether, such alterations directly or indirectly change the availability of substrates, other than glucose, to the fetus either by increasing their source or by modifying the materno-fetal interface. Additionally, placental epigenetic changes were recently reported at gene loci involved in energy metabolism regulation like those of adipokines.²⁰ This epigenetic adaptation to detrimental *in utero* environment may have impacts on the short- and long-term metabolic regulations of the newborn. Maternal pregestational overweight or obesity that frequently associated with GDM or T2D may also increase lipid availability, modulate delivery of lipid substrates to the fetus, and have programming consequences.

In a multiethnic group, youth aged 10–22 years with T2D were more likely to have been exposed to maternal diabetes or obesity. Exposure to maternal diabetes (OR 5.7 [95% CI 2.4–13.4]) and exposure to maternal obesity (2.8 [95% CI 1.5–5.2]) were independently associated with T2D in the offspring. Exposure to maternal diabetes *in utero* resulted in an attributable risk of only 4.7%, although 47.2% of T2D in youth could be attributed to intrauterine exposure to maternal diabetes and obesity together.²¹

Concerning the link between *in utero* diabetes and overweight and obesity in offspring, the literature provides contradictory results. Although *in utero* exposure to maternal diabetes plays a role in the occurrence of overweight in the offspring, the importance and the respective significance of the exposure to GDM relative to other risk factors associated with maternal diabetes (genetic, maternal overweight, fetal macrosomia, lifestyle, socioeconomic) have been poorly quantified. After adjusting on maternal prepregnancy BMI, the association between maternal diabetes and offspring BMI was no longer significant in some studies.^{22,23} Although convincing data exist in the literature on the effect of maternal diabetes on offspring health, many unanswered questions remain regarding the size effect of maternal intrauterine exposure compared with shared genetic traits. These, in turn, are difficult to distinguish from influences of the child's postnatal environment and lifestyle.

Effect of high birth weight on long-term outcomes

Maternal diabetes is one of the main risk factors of having macrosomic infants at birth. A number of publications have reported the link between high birth weight (BW) and obesity in childhood to early adulthood. A meta-analysis showed

that BW ≥ 4000 g increases twofold the risk for obesity, and this risk is increased about 2.5-fold when BW exceeds the 90th percentile.²⁴ However, the association between higher BW and higher adult BMI may be due to increased lean mass rather than an increase in fat tissue. Evidence suggests that although BW is positively associated with BMI, it is not necessarily associated with increased adiposity, and at higher BW, subsequent adiposity may actually be reduced.²⁵

Being large for gestational age (LGA, BW > 90th percentile), in association with GDM or maternal obesity, increases the risk of MS in childhood. A longitudinal cohort study analyzed the prevalence of MS in children aged 6–11 years, accordingly they were LGA or adapted for gestational age (AGA, BW 10th–90th percentile), and their mothers had or had no GDM. The prevalence at any time of at least two components of MS was higher for the LGA/GDM group (50%), compared to the LGA/control group (29%), AGA/GDM group (21%), and AGA/control group (18%). The risk of developing MS with time was significantly different between LGA and AGA offspring in the GDM group, with a 3.6-fold greater risk among LGA children by 11 years. In this study, children exposed to maternal obesity were also at increased risk of developing MS.²⁶

A recent systematic review on the association between BW and risk of T2D showed that in most populations studied, BW was inversely related to T2D risk. There was a positive association between high BW (>4 kg) and risk of T2D only in two native North American populations. These populations have an exceptionally high prevalence of T2D and obesity from early ages and a very high prevalence of GDM. Therefore, the influence of maternal diabetes/obesity on the BW–T2D association could not be excluded in these populations and may overweight the effect of being LGA alone.²⁷

Effect of maternal glycemic and gestational weight gain control on long-term prognosis in the offspring

Treatment of GDM may be an important determinant of offspring outcomes, but there is currently insufficient information to firmly assess the effects of maternal interventions on infant and child health. Two trials are available in the literature, with a follow-up of offspring of mothers randomized to either minimal intervention or tight control of diabetes.^{28,29} They did not demonstrate any differences in the frequency of MS or in the weight of the children according to the intervention provided to their mothers.

In a large cohort of 9439 mother–child pairs in a diverse US population universally screened for GDM, it was shown that increasing hyperglycemia levels in pregnancy were associated with increased risk of obesity in children at age 5–7 years. But this risk was modifiable by treating GDM, as obesity risk was attenuated and no longer significant after multivariate adjustment in the treated GDM group.³⁰

There are significant methodological difficulties in proving an effect of maternal glycemic control over the long

term because it may not be sufficient alone to prevent the adverse long-term outcome on the offspring.¹⁷ As discussed earlier, other substrates influence fetal growth and probably have long-term metabolic consequences. Excess gestational weight gain (GWG) is a factor associated with high BW and subsequent long-term outcomes. The comparison of differences in BW between sibling pairs showed that for every additional kilogram an individual woman gained during pregnancy, the BW of her offspring increased by about 25 g.³¹ In a large prospective multicentric study, excessive GWG was an independent valuable predictor of macrosomia. In the subgroup of diabetic mothers, excessive GWG (according to the Institute of Medicine [IOM] recommendations) was related to a 2.6-fold increased risk of developing macrosomia (OR 2.6; 95% CI 1.2–5.5). However, in this population, GWG lower than recommended was not associated with a reduction of macrosomia (OR 0.8; 95% CI 0.3–1.8).³² In a large Swedish prospective cohort, offspring BMI was related to maternal GWG. However, in normal-weight women, this positive association was only driven by shared familial risk factors for BMI (genetic/environment). In overweight and obese women, a greater maternal GWG appears to be associated with greater offspring BMI via intrauterine mechanisms and shared familial characteristics.⁴

Maternal weight gain during pregnancy is probably an important and challenging modifiable risk factor because excessive GWG is associated with higher BW. The absence of effect of reduced GWG on fetal growth in diabetic pregnancy, reported in some studies, may be due to the fact that IOM guidelines were not conceived for diabetic mother. Then, the challenge is to determine nutritional guidelines specifically devised for women with diabetes, considering the amounts of calories but also the quality of nutrients.

Other factors of prevention (prepregnancy control of overweight, regular activity, etc.) must be recommended to the mother as part of a comprehensive management plan.

Effect of breastfeeding

Infancy has been suggested as another critical period for future risks in the offspring whatever was the intrauterine environment. Breastfeeding compared with formula feeding showed to have beneficial effects on glucose tolerance, HT, dyslipidemia, and obesity.³³ The strongest evidence for a protective effect of breastfeeding for later health is for a lower risk of obesity. Although unknown, some potential mechanisms by which breastfeeding protects against later risk have been discussed. Breastfed babies may control the amount of milk they consume and so learn to self-regulate their energy intakes better than those given formula, although whether this difference persists into adult life is unknown. Nutritional benefits of breastfeeding may include differences in nutrients between human milk and formulas (lower glucose and protein, high concentrations in long-chain polyunsaturated fatty acid). Differences in early protein intakes that are greater in formula than in human milk could also affect later adiposity. It has been suggested that the benefits of breastfeeding for long-term obesity is of particular

importance in the early postnatal weeks of life. This is a critical period for determining levels and distribution of adiposity. The benefits of breastfeeding at this time may be due to a slower pattern of growth in breastfed compared with formula-fed infants (the growth acceleration hypothesis).³⁴ Weight gain during the first week of life in healthy formula-fed infants was associated with overweight status two to three decades later. After adjustment for important confounding factors, each 100 g increase in absolute weight gain during this period was associated with a 28% increase in the risk of becoming an overweight adult (95% CI 8%–52%).³⁵ A long-term advantage of breastfeeding was further supported by a “dose–response” effect. A longer duration of breastfeeding was associated with a lower tendency to later obesity; each month of breastfeeding was associated with a 4% (95% CI –6% to –2%) reduction in obesity risk.³⁶

In diabetic mothers, there are many controversies concerning breastfeeding benefits in their offspring, particularly during the first week of life. Some observed a positive dose-dependent relation between the volume of diabetic mother milk ingested during the first neonatal week and later risk of overweight.³⁷ But those infants who did not receive breast milk from their diabetic mothers were instead nourished with banked breast milk from nondiabetic donor mothers. This created a different “reference exposure” than in all other studies where breastfeeding was tested against formula. The mechanisms evoked for such a negative effect of breast milk from diabetic mothers was that it contains increased levels of glucose and insulin as compared with breast milk from healthy mothers but even hormones like insulin and leptin that may be absorbed from milk in the immature gut of an infant.³⁸ However, the composition of milk from diabetic mothers may also be influenced by metabolic control during pregnancy and postpartum, and this may change the impact on the outcome of offspring. The same authors found that neither late neonatal intakes of breast milk from diabetic mothers nor the duration of breastfeeding has an independent influence on childhood risk of overweight or glucose intolerance.³⁹ However, others found that adequate breastfeeding (≥ 6 months) reduces, in childhood, the increase of adiposity levels associated with exposure to diabetes in utero.⁴⁰ Furthermore, these results were strengthened by the follow-up of a longitudinal cohort. It was shown that adequate breastfeeding reduced the overall body size and slowed

BMI growth velocity both during infancy and in the childhood period, in offspring of nondiabetic mothers, as well as in offspring of diabetic mothers. These effects were independent of sex, race/ethnicity, current childhood diet, and physical activity levels. This study indicates that the favorable effects of breastfeeding on BMI growth patterns extend throughout the entire childhood period and are also present in youth at increased risk for obesity due to intrauterine exposure to maternal diabetes.⁴¹ Others have reported data that favor the benefit of breastfeeding in offspring of diabetic mothers, either on the risk of obesity⁴² or on the risk of diabetes.⁴³

Overall, there is no doubt that breastfeeding should be recommended in diabetic mothers, all the more since GDM and T2D are increasingly spreading in emerging countries. The controversies concerning the benefit of breastfeeding in diabetic mothers should be reviewed in the light of potential confounders, especially the time point of exposure, exposure quality (exclusive or not exclusive breastfeeding), and duration, but also ethnicity, socioeconomic status, and maternal BMI. Breastfeeding may represent an important challenge in preventing long-term disorders in the offspring of diabetic mothers.

Conclusion

More and more indisputable data are evidencing long-term consequences on offspring health in case of gestational diabetes or excess growth at birth. Converging results from clinical and epidemiological data, but also from animal models (see Chapter 10), suggest that GDM contributes to the current worldwide T2D pandemic. However, the specific mechanisms remain unclear and many aspects, in particular epigenetic, need to be clarified. The specific intrauterine metabolic alterations that favor such long-term evolution need to be investigated, and the consequences of overweight and obesity among those of diabetes should be separately evaluated. Such comprehensive data will offer major proved opportunities for prevention. Meanwhile, obvious preventive measures are indicated like early diagnosis and tight control of maternal diabetes during pregnancy, limited GWG, and promotion of breastfeeding.

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62 Metabolomics and diabetic pregnancy

Angelica Dessì, Roberta Carboni, and Vassilios Fanos

Introduction

Diabetes is one of the diseases that most frequently complicate the course of pregnancy, especially in developed countries where the increased incidence of obesity is one of the risk factors.¹

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset, or which is recognized for the first time, during pregnancy. In some cases, it is a pregestational diabetes revealed by investigations during pregnancy, but in other cases it is diabetes with onset during pregnancy; the latter represents 90% of pregnancies complicated by diabetes.²

GDM is a disease that has important repercussions on both the mother and the child, and, therefore, early diagnosis and timely treatment may avoid acute and chronic complications for both.³

At present, the only laboratory method for the diagnosis of gestational diabetes is glycemia measurement. However, this is a method that does not take into account the overall metabolic condition of the organism and that is often performed at an advanced stage of pregnancy. Moreover, there are still no methods that are useful in singling out women at greater risk of developing GDM and assessing the effectiveness of therapy in single patients.

Metabolomics, thanks to its capacity to investigate the overall metabolic state of an entire organism, appears to be a promising technique also in the study of GDM and the recognition of possible new biomarkers to reveal at an early stage the women at higher risk of developing this pathological condition.

Diabetic pregnancy

Definition

By GDM is meant a condition characterized by a reduced tolerance to glucides, with hyperglycemia of varying seriousness that begins during pregnancy.⁴ The definition is applied regardless of the use of insulin in the treatment or persistence of the condition following the pregnancy.

Thus, the possibility that glucose intolerance may be prior to or begin during pregnancy cannot be excluded.⁵ This pathology has a prevalence of 3%–10% and represents approximately 90% of all pregnancies complicated by diabetes.^{2,6} Moreover, the increase in maternal age, the high incidence of obesity and diabetes, and the reduction of physical activity with the adoption of modern lifestyles in developing countries have contributed to an increase in the prevalence of GDM.⁷

Pathophysiology and etiopathogenesis

Pregnancy is a condition during which a certain degree of insulin resistance develops physiologically, especially in the muscle and adipose tissues, to ensure fetal growth.⁸ In the maternal organism, there is a decreased use of insulin-mediated glucose that favors an increase in carbohydrates for the fetus.⁹ In a physiological pregnancy, the basal glycemia remains constant up to the last 3 months and carbohydrate intolerance develops only when β -cell secretion is no longer capable of compensating for peripheral insulin resistance.¹⁰ Most of the evidence points to a defect in the β -cell if the GDM is more than acute. The hypothesis that the β -cell defect is chronic suggests that when GDM is diagnosed, it includes some women with a preexistent glucose intolerance revealed by tests performed during pregnancy.

From the etiopathogenetic viewpoint, GDM is considered a type 2 diabetes. GDM is frequently characterized by reduced insulin secretion accompanied by an increase in peripheral insulin resistance, two conditions typical of type 2 diabetes. During pregnancy, the variations in insulin secretion depend on endocrine alterations that accompany pregnancy. Changes in β -cell function take place at the time of development of the fetus and placenta and the production of hormones such as the human chorionic growth hormone, progesterone, cortisol, and prolactin.

These hormones in a woman with GDM are capable of causing insulin resistance, high triglyceride levels, and lower HDL cholesterol levels compared to what is observed in women with physiological pregnancies.¹¹

In GDM patients, insulin secretion is incapable of compensating for the insulin resistance characteristic of

pregnancy. Therefore, the loss of the first phase of insulin secretion will cause postprandial hyperglycemia, while the reduced suppression of hepatic production of glucose will be responsible for fasting hyperglycemia.

Diagnosis

As concerns diagnosis, guidelines recommend the measurement of blood sugar at the first appointment in pregnancy for all women with no previous tests to single out those with diabetes prior to becoming pregnant; also recommended is the screening for diabetes in cases of physiological pregnancy using defined risk factors.

At the 16th–18th week of gestation, an OGTT with 75 g of glucose and a second OGTT with 75 g at 28 weeks of gestational age if the first test gave a normal result should be performed on all women presenting at least one of the following conditions:

- Gestational diabetes in a previous pregnancy
- Prepregnancy body mass index (BMI) ≥ 30
- The finding of blood sugar values between 100 and 125 mg/dL (5.6–6.9 mmol/L) previous to or at the beginning of pregnancy

At the 24th–28th week of gestational age, women presenting at least one of the following conditions must undergo a 75 g OGTT:

- Age ≥ 35 years
- Prepregnancy BMI ≥ 25 kg/m²
- Fetal macrosomia in a previous pregnancy (≥ 4.5 kg)
- GDM in a previous pregnancy (even with a normal result at the 16th–18th week)
- Family anamnesis of diabetes (first-degree relative with type 2 diabetes)
- Family from an area with a high rate of diabetes: Southern Asia, the Caribbean, and the Middle East

Based on the results of this screening, women with fasting glycemia ≥ 92 mg/dL, after 1 hour ≥ 180 mg/dL, and after 2 hours ≥ 153 mg/dL are defined as affected by GDM. The guidelines also specify that in screening for GDM, the following are not to be used: fasting blood sugar, random glycemias, glucose challenge test (GCT) or minicurve, glycosuria, and OGTT 100 g.¹²

Acute and chronic consequences for mother and child

GDM causes an increased risk of morbidity in the fetus and neonate and may be the cause of a later development of type 2 diabetes, in both the mother and the child.¹³ We can distinguish early and late complications in connection with the maternal pathology that will involve mother and child. As concerns the mother, early complications are represented by the risk of spontaneous abortion, polyhydramnios, hypertension in pregnancy, pyelonephritis and other infections, preterm delivery, hypoglycemia, ketoacidosis, and cesarean delivery. The late complications for the mother are in

relation to the fact that GDM may be the first manifestation of a type 2 diabetes or a metabolic syndrome; thus after pregnancy, it is important for these women to be followed up.¹⁴

The early complications for the neonate are respiratory distress, shoulder dystocia, hyperbilirubinemia, polycythemia, hypocalcemia, macrosomy, and hypoglycemia; the late ones are instead connected with a higher risk of overweight and obesity in the adolescent age as well as the higher risk of developing type 2 diabetes, this too in the adolescent period.

The reduced action of insulin in GDM causes an excessive increase of nutrients in the blood (glucose, lipids, amino acids), which, on passing through the placenta, determine hyperinsulinism capable of favoring a consequent increase in adipose tissue with fetal organomegaly and macrosomia.¹⁰ On passing through the placental barrier, the excess maternal glucose causes a condition of constant hyperglycemia in the fetus that will lead to chronic hyperinsulinism that, on continuing after delivery, will result in neonatal hypoglycemia.¹⁵ This reduced glucidic tolerance will tend to persist during growth and into adulthood and consequently will expose the children of diabetic mothers to a higher risk of developing pathologies such as obesity and type 2 diabetes.

Metabolomics

Metabolomics, one of the most recent of the omics sciences, is defined as the study of the complex system of metabolites owing to its capacity of examining an individual's entire metabolic profile.

A metabolomic analysis is capable of detecting analytes of relatively low molecular weight (up to 1000 Da), among which amino acids, oligopeptides, sugars, steroids, biliary acids, simple and compound fatty acids, and intermediate compounds of many biochemical pathways.¹⁶ The metabolomic approach consists of the sequential application of a surveying technique with the use of nuclear magnetic resonance (NMR) and gas or liquid chromatography coupled with mass spectrometry (LC-MS and GC-MS), by means of which it is possible to measure simultaneously the concentration of a large number of metabolites in the sample. The most common biological samples used in metabolomics are urine, plasma, and serum, but other biofluids can be used as well (liquor, saliva, gastric/pancreatic juices, aqueous humor) or tissues. Each biological fluid has a unique and characteristic biochemical composition that changes in response to physiological or pathophysiological stimuli to generate a metabolic “fingerprint.” This discipline, based on the use of mathematical and statistical methods to solve multivariate problems, is capable of describing the chemical profile of a biological system in terms of low-molecular-weight metabolites present in cells, tissues, organs, and biological fluids.

By means of a metabolic approach, it is thus possible to photograph “in real time” the influences on the organism such as biochemical perturbations caused by diseases, drugs, and toxins, thus describing the biochemical phenotype of a biological system.¹⁷

In recent years, many clinical studies have been performed on animals, adults, children, and neonates using a metabolomic approach that makes it possible to study important perinatal and postnatal pathologies such as asphyxia and hypoxia, congenital diseases, the state of nutrition, kidney diseases, nephrotoxicity, cardiovascular disease, and other pathologies.^{18–20} In the medical field, there is growing interest in characterizing at the biochemical and molecular level the different pathophysiological states that mark the lives of human beings in the period from embryonic development to ageing and death. “Clinical metabolomics” is proposed as a new multidisciplinary scientific field developed through the interaction of disciplines such as chemistry, physics, biology, and medicine, which to the same extent contribute to the gathering of up-to-now latent information, leading to the identification of new phenotypical characteristics of diseases studied but not yet adequately defined. The ultimate objective of such characterization is that of developing “tailored” therapeutic approaches for the single individual and/or group of individuals, where for group is meant persons having a common phenotypical profile deriving from a similar gene–environment interaction.^{21,22}

Gestational diabetes and metabolomics

As can be seen in the guidelines, at present the diagnosis of GDM is based solely on the finding of high values of glucose in the blood. This kind of investigation does not take into consideration the complete metabolic picture of a woman as well as being, in cases not considered at risk, performed toward the end of the 6 month of pregnancy when, if it is found altered, the fetus is already affected by a series of metabolic influences capable of impacting on its growth.

For this reason, the application of an “alternative” method is necessary to help in characterizing the overall metabolic state of a pregnant woman. Metabolomics in the field of this pathology would appear to be the most suitable method since it is capable of providing a quantitative measurement as a function of time of the metabolic response of a living system to pathophysiological stimuli and/or genetic modifications.¹⁶

As concerns GDM, metabolomics proposes to identify biomarkers useful in predicting, already at an early stage of gestation, if a woman is prone to GDM and thus beginning timely treatment so that the disease does not develop and that the fetus does not undergo any of the mother’s metabolic influences that may impact on its metabolism and growth.

Moreover, thanks to metabolomics, it is possible to study more in depth the metabolic profile of pregnant women.

Up to the present, few works have been published on the application of metabolomics to the study of women presenting GDM and the assessment of the metabolic state of the children of GDM mothers (Table 62.1), but the results appear promising both as regards the overall metabolic state of women and their risk of developing GDM and as regards the metabolic profile of the neonate.²³

In the literature, we find four studies that focused on the metabolomic analysis of maternal biofluids in women presenting GDM and two studies that assessed the metabolome of the children of diabetic mothers.

The study by Sachse et al.¹⁴ examined the urinary metabolic profile by means of NMR of pregnant women for the purpose of identifying biomarkers useful in identifying the women most at risk of developing GDM. The urinary metabolic profiles of 823 pregnant women in good health were analyzed. Urine samples were taken in the morning while fasting and during three different visits: from the 8th to the 20th week of pregnancy, from the 26th to the 30th week, and from 10 to 16 weeks after delivery. The authors highlighted the substantial changes in the composition of the urinary metabolites during and after the pregnancy; in particular, the most important results were the constant increase in lactose and the increasing–decreasing pattern of a plurality of NMR signals between 0.55 and 1.10 ppm, signals that may belong to pregnanediol and estrogens, or more probably, to their sulfates and water-soluble glucuronoids.

As concerns the possibility of finding biomarkers capable of identifying GDM, the authors concluded that on the basis of their results, it is not possible to find reliable biomarkers for GDM in a large multiethnic population; however, an increase in the citrate excreted in the urine in relation to the seriousness of the cases of GDM was found.

The work by Diaz et al.²⁴ was performed on urine and plasma of women in the final 3 months of pregnancy in an

Table 62.1 Studies in the literature concerning metabolomics and GDM

Study	Sample	Population	Metabolomic analysis	Metabolites resulting
Dani et al. ²⁸	Cord serum	Infants	1H-NMR	Glucose, pyruvate, histidine, alanine, valine, methionine, arginine, lysine, hypoxanthine
Logan et al. ²⁷	Urine	Infants	1H-NMR	Glucose, formate, fumarate, succinate, citrate
Graça et al. ²⁶	Urine, amniotic fluid	Mothers	UPLC-MS 1H-NMR	None
Sachse et al. ¹⁴	Urine	Mothers	1H-NMR	Lactose, citrate
Diaz et al. ²⁴	Urine, plasma	Mothers	1H-NMR	3-Hydroxyisovalerate, 2-hydroxyisobutyrate
Scioscia et al. ²⁵	Urine	Mothers	MS	Inositolphosphoglycan P-type

attempt to characterize metabolic changes possibly caused by prenatal disorders and identify possible early biomarkers of diseases. The metabolic profile was analyzed by means of NMR and the metabolomic analysis revealed higher levels of 3-hydroxyisovalerate and 2-hydroxyisobutirrate in the urine of women who later developed GDM.

The work by Scioscia et al.²⁵ assessed by means of a metabolomic approach performed with MS on the urine of pregnant women if inositolphosphoglycan P-type (P-IPG), a second insulin messenger that correlates with the degree of resistance in diabetic subjects, may have changed during pregnancy. The study examined 48 women with GDM and 23 healthy women during pregnancy and revealed an increase in urinary excretion of P-IPG in the GDM women compared to controls. The authors also found a correlation between urinary values of P-IPG and blood glucose. According to the authors, the metabolomic identification of P-IPG is a potential marker of insulin resistance and may predict fetal growth alteration in GDM patients.

Finally, the study by Graça et al.²⁶ was performed on urine and amniotic liquid of women in the second 3 months of pregnancy with the use of both the UPLC-MS and 1H-NMR methods. The authors investigated the possible metabolic effects of fetal malformations, GDM, and preterm delivery. In particular, contrary to the other works published, in the metabolome in the case of GDM, no significant changes were found, either in the urine or in the amniotic liquid.

The other two studies in the literature examined the fetal metabolism of neonates of GDM mothers to assess the consequences of the maternal pathology on the development of their children.

In their study, Logan et al.²⁷ hypothesized that the metabolic profile of the neonates of diabetic mothers (IDM) was different from that of children of healthy mothers. They then studied the metabolome of 18 IDM neonates and 12 term and healthy neonates used as controls. Urine was collected within 72 hours from birth using balls of absorbent cotton and then conserved at -80°C ; the metabolomic analysis was then performed by means of 1HNMR spectroscopy and the spectra obtained were analyzed using

MATLAB[®] software*. The statistical analysis was performed with the principal component analysis (PCA) and partial least square-discriminant analysis (PLS-DA). The results obtained in this study made it possible to discriminate between the two groups of neonates: the most important differences in the urinary metabolites were those found for glucose, formate, fumarate, citrate, and succinate, all metabolites involved in the tricarboxylic acid cycle.

Another similar work was carried out by Dani et al.,²⁸ who studied the metabolome of newborn children of GDM mothers and compared it with that of the neonates of healthy mothers. The purpose of the study was to see if there were differences between the two groups and if such differences remained evident despite close control over the GDM.

The metabolomic analyses with 1HNMR were performed on the serum of 30 IGDM term neonates and 40 term neonates of healthy mothers used as controls. The results of these investigations revealed a lower level of glucose and a higher level of pyruvate, histidine, alanine, valine, methionine, arginine, lysine, hypoxanthin, lipoproteins, and lipids in the neonates of GDM mothers compared to the controls. Despite these variations, the authors found no differences from the clinical standpoint.

Conclusions

A new challenge in medicine is certainly the application of metabolomics in the study of pathologies originating in the womb that may later lead to both short- and long-term complications, as in the case of GDM. The studies published show that metabolomics can be considered a potential and formidable instrument for prevention by identifying women most at risk of developing GDM. An evaluation of this kind would make it possible to indicate a therapy, a lifestyle, and diet to follow in pregnancy so as to avoid the frequent complications caused by GDM.

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63 Fetal growth restriction: Evidence-based clinical management

Eduard Gratacós and Francesc Figueras

Introduction

Fetal growth restriction (FGR) is defined as a failure to achieve the endorsed growth potential. The diagnosis of fetal “smallness” is currently performed on the basis of an estimated fetal weight below a given threshold, most commonly the 10th centile. It is likely that this definition lacks sensitivity, so that it misses cases of growth restriction that do not fall below the 10th centile, but it identifies a subset of pregnancies at high risk of poorer perinatal outcome. Thus, detection of small fetuses is clinically relevant because as a whole this group of fetuses is associated with poorer perinatal outcome, and this represents opportunities for preventing cases of intrauterine fetal death, perinatal brain injury, and severe intrapartum fetal distress. In addition, evidence accumulating over the last 20 years has consistently demonstrated how being born small has important implications for the quality of health during adulthood. Population-based studies show that prenatal identification of small for gestational age (SGA) results in a reduction of adverse perinatal outcomes and stillbirth.^{1,2} However, most SGA babies remain unnoticed until birth, even when routine third trimester ultrasound is performed.^{3,4} Moreover, according to pregnancy audits, most instances of avoidable stillbirth are related with a failure to antenatally detect SGA.⁵ However, FGR is probably among the obstetrical entities with the greatest variation in clinical management, resulting from lack of strong supportive evidence, combined with the complexity of the variables and indices for assessing fetal deterioration.

In this chapter, we will summarize the main aims in the clinical management of FGR, which should be (1) to distinguish “true” FGR from constitutional SGA and (2) to establish whether there is an indication for elective delivery and if not how often monitoring should be performed.

“Fetal growth restriction” versus “small for gestational age”

Overall, a “small fetus” is associated with poorer outcome. However, evidence shows that there are, at least, two groups of small fetuses, normally referred to as FGR versus constitutional SGA, also defined as just SGA. FGR is associated with poorer perinatal outcome, abnormal Doppler suggesting fetal adaptation to undernutrition/hypoxia, signs of placental disease, and higher risk of preeclampsia (PE). SGA fetuses do not present the aforementioned changes and display perinatal outcomes similar to those of normally grown fetuses. It is unknown whether SGA fetuses are truly “constitutionally small” or they represent another form of fetal abnormal smallness. The distinction between FGR versus SGA is clinically relevant because of the wide consensus that it is reasonable to deliver electively FGR earlier, whereas elective delivery before term offers no benefit in SGA.

The diagnosis of FGR is currently performed by means of a combination of Doppler and estimated fetal weight. For 20 years, the Doppler index widely used to distinguish FGR from SGA was abnormal umbilical artery (UA) Doppler. However, UA Doppler identifies severe placental disease but fails to pick up instances of mild placental disease, which in reality constitute the majority of cases of FGR.^{4,6} Thus, UA Doppler should always be used in combination integrated in the cerebroplacental ratio (CPR). CPR is calculated by dividing the middle cerebral artery (MCA) Doppler pulsatility index (PI) by the UA Doppler PI. This index correlates better with adverse outcome.⁷ Aside from CPR, both the uterine artery Doppler PI (UtA PI)⁸ and a very low EFW (<p3)⁹ have been shown to independently predict poorer outcome in small fetuses. Thus, the definition of FGR should include these three parameters, and we have provided good evidence

that, when used in combination, the presence of at least one of these signs can classify as the subgroup of small fetuses with the highest risk of poor perinatal outcome.¹⁰ It is likely that in future years, composite definitions include angiogenic factors as a valid criterion,¹¹ but the lack of normative gestational-age-adjusted values is for the moment a limitation for its wide use in practice.

Finally, we should stress that SGA is associated with apparently near-normal perinatal outcomes. However, in the light of current evidences, SGA is not a “constitutionally” small fetus. Fetuses under this diagnostic category have been consistently demonstrated to present signs of brain reorganization in utero and neonatally and poor long-term neurological, cardiovascular, and endocrinological outcome.^{12–14} Therefore, the so-defined SGA fetuses are, in the majority of instances, suffering a form of pathological deviation from normal development. It remains to be established whether SGA is a category composed by a single problem or a mixture of different causes, which might include among others a subset of fetuses with placental insufficiency of even milder nature, abnormalities in hormonal pathways regulating fetal growth, genetic causes, and true constitutional smallness.

“Early-onset” versus “late-onset” FGR

Aside from the clinically relevant distinction between FGR and SGA, FGR presents under two different phenotypes when the onset is early or late in gestation. Table 63.1 displays the main differences between both clinical forms. Differentiating between early- and late-onset FGR has a clear value and should always be required for any research study for the sake of comparability. Being early or late onset determines differences in the severity of placental disease,¹⁵ as well as in the fetal adaptive response and deterioration. These notions have been extremely important for our pathophysiological understanding of the various clinical presentations of FGR. However, when clinical decisions are

at stake, the distinction into “early” or “late” is too simple and difficult to integrate since the determinants of elective delivery are the severity of fetal deterioration and the risks of prematurity. For this reason, in our view FGR is better managed with a single protocol throughout pregnancy, as discussed later in this chapter. The cutoff to define early-versus late-onset FGR has commonly been set in an arbitrary fashion at about 32–34 weeks at diagnosis or 37 weeks at delivery. A prospective study using decision tree analysis in >700 cases determined that 32 weeks at diagnosis and 37 weeks at delivery best classified two groups where the differences in terms of adverse perinatal outcome are maximized.¹⁶

Briefly, early-onset FGR represents about 20%–30% of all FGR and it is associated with early PE in up to 50%.⁴ In early-onset FGR, there is commonly severe placental insufficiency and chronic fetal hypoxia; hence UA Doppler is usually abnormal.¹⁷ Fetal condition deteriorates with evolution to decompensated hypoxia and acidosis, which is reflected by progression of abnormalities in the UA into absent and reverse diastolic flow and increased PIs in the ductus venosus (DV), which is used as a reflection of late-stage disease and very high risk of fetal death. Fetal deterioration normally lasts weeks¹⁸ following a cascade of Doppler changes. Management is challenging and aims at achieving the best balance between the risks of leaving the fetus in utero versus the complications of prematurity.

Late-onset FGR represents 70%–80% of FGR and has a low association (about 10%) with late PE.¹⁹ The degree of placental disease is mild;²⁰ thus UA Doppler is below the 95th centile in virtually all cases.⁶ However, the CPR, which combines changes in the UA and MCA, becomes abnormal at some point before birth in a substantial proportion of cases.⁶ Changes in the DV are virtually never observed,^{6,21} and the cascade of sequential fetal deterioration described for early onset does not occur in late FGR. However, progression to fetal deterioration may occur suddenly and there is high association with intrapartum fetal distress and neonatal acidosis.^{22,23} We have proposed²⁴ that this is possibly the consequence of a combination of rapid placental function deterioration, lower tolerance to hypoxia in term fetuses, and the more frequent presence of intense uterine contractions at this pregnancy stage.

Table 63.1 Summary of the main differences between early- and late-onset forms of fetal growth restriction

Early-onset FGR	Late-onset FGR
Challenge: Management	Challenge: Diagnosis
Prevalence: 1%–2%	Prevalence: 3%–5%
Severe placental disease: UA Doppler abnormal, high association with PE	Mild placental disease: UA Doppler normal, low association with PE
Severe hypoxia ++: systemic CV adaptation	Mild hypoxia: central CV adaptation
High mortality and morbidity	Lower mortality (but common cause of late stillbirth)
Abbreviations: PE, preeclampsia, CV, cardiovascular.	

Fetal assessment and correlation with perinatal outcomes

Some of the measures and indices discussed later are essentially used for the diagnosis/identification of FGR from SGA, and consequently, they are relevant for the decision as to whether delivery is indicated when pregnancy term is reached. Another set of indices have a prognostic value, since they are useful to determine that there is a high risk of deterioration, and consequently, they are used to indicate delivery before term is reached.

Umbilical artery Doppler

UA Doppler is the only measure that provides both diagnostic and prognostic information for the management of FGR. There is compelling evidence that using UA Doppler in high-risk pregnancies improves perinatal outcomes, with a 29% reduction in perinatal deaths.²⁵ Absent or reversed end-diastolic velocities, the end of the spectrum of the abnormalities of the UA Doppler, have been reported to be present, on average, 1 week before the acute deterioration.²⁶ There is an association between reversed end-diastolic flow in the UA and adverse perinatal outcome (with a sensitivity and specificity of about 60%), which seems to be independent of prematurity.²⁷ After 30 weeks, the risk of stillbirth of a fetus with isolated reversed end-diastolic velocities in the UA Doppler overcomes the risks of prematurity,^{28,29} and therefore delivery seems justified.

Middle cerebral artery Doppler/cerebralplacental ratio

MCA informs about the existence of brain vasodilation, a surrogate marker of hypoxia. There is an association between abnormal MCA-PI and adverse perinatal and neurological outcome, but it is unclear whether delivering before term could add any benefit. MCA is particularly valuable for the identification of⁶ and prediction of adverse outcome among^{30,31} late-onset FGR, independently of the UA Doppler, which is often normal in these fetuses. Fetuses with abnormal MCA-PI had a sixfold risk of emergency cesarean section for fetal distress when compared with SGA fetuses with normal MCA-PI,³² which is particularly relevant because labor induction at term is the current standard of care of late-onset FGR.^{33–35} Late-FGR with abnormal MCA-PI has poorer neurobehavioral competence at birth and at 2 years of age.^{23,36} MCA is considered a rather late manifestation, with acceptable specificity but low sensitivity, which is improved by the use of CPR.

The CPR improves remarkably the sensitivity of UA and MCA alone. Thus, the CPR is already decreased when its individual components suffer mild changes but are still within normal ranges.^{37,38} In late-onset SGA fetuses, abnormal CPR is present before delivery in 20%–25% of the cases,³⁹ and it is associated with a higher risk of adverse outcome at induction, although to a lesser degree than MCA.³²

Ductus venosus Doppler

DV is the strongest single Doppler parameter to predict the short-term risk of fetal death in early-onset FGR. Longitudinal studies have demonstrated that DV flow waveforms become abnormal only in advanced stages of fetal compromise.^{18,26,27,40} Absent-reversed velocities during atrial contraction are associated with perinatal mortality independently of the gestational age at delivery,⁴¹ with a risk ranging from 40% to 100% in early-onset FGR.^{35,42} Thus, this sign is normally considered sufficient to recommend delivery at any gestational age, after completion of steroids. In about 50%

of cases, abnormal DV precedes the loss of short-term variability in cCTG, and in about 90% of cases, it is abnormal 48–72 hours before the biophysical profile (BPP).^{18,40} Hence, it is considered to provide a better window of opportunity for delivering fetuses in critical conditions at very early gestational ages.

Aortic isthmus Doppler

This vessel reflects the balance between the impedance of the brain and systemic vascular systems.^{43,44} Reverse aortic isthmus (AoI) flow is a sign of advanced deterioration and a further step in the sequence starting with the UA and MCA Doppler. AoI has a strong association with both adverse perinatal⁴⁵ and neurological outcome.⁴⁶ However, longitudinal studies show that the AoI precedes DV abnormalities by 1 week,^{21,47} and consequently it is not as good to predict the short-term risk of stillbirth.³⁵ In contrast, AoI seems to improve the prediction of neurological morbidity.³⁰

Fetal heart rate analysis and biophysical profile

Early studies on high-risk pregnancies showed that, though highly sensitive, cardiotocography has a 50% rate of false positives for the prediction of adverse outcome.⁴⁸ In addition, a meta-analysis⁴⁹ on high-risk pregnancies failed to demonstrate any beneficial effect in reducing perinatal mortality. Hence, there is no evidence to support the use of traditional fetal heart rate (FHR) monitoring or “nonstress tests” in FGR fetuses. A main limitation of CTG is the subjective interpretation of the FHR, which is extremely challenging in very preterm fetuses with a physiologically reduced variability. cCGT has represented a step forward and has provided new insights into the pathophysiology and management of FGR. cCGT evaluates short-term variability of the FHR, an aspect that subjective evaluation cannot assess. Current evidence suggests that cCGT is sensitive to detect advanced fetal deterioration, and it provides a value similar to DV reverse atrial flow for the short-term prediction of fetal death. Short-term variability becomes abnormal, coinciding with the DV, whereas in about half of cases, abnormal DV precedes the loss of short-term FHR variability; the latter is the first to become abnormal in the other cases.¹⁸

Concerning BPP, it is calculated by combining ultrasound assessment of fetal tone and respiratory and body movements, with amniotic fluid index (AFI), and a conventional CTG. BPP was designed to improve the performance of FHR. Early observational studies reported a very low risk of false positives for acidosis and perinatal death, but more recent studies on early-onset very preterm FGR fetuses raise concerns over the false-positive rate, with up to 23% of instances of IUFD in fetuses with BPP > 6 and 11% in those with BPP > 8.⁵⁰ A meta-analysis⁵¹ showed no significant benefit of BPP in high-risk pregnancies. Consequently, whenever Doppler expertise and/or cCTG is available, the incorporation of BPP in management protocols of FGR is questionable.

Amniotic fluid index

AFI is used essentially as part of the BPP. Amniotic fluid volume is believed to be a chronic parameter. In fact, among the components of BPP, it is the only one that is not considered acute. A meta-analysis⁵² of 18 randomized studies demonstrated that a reduced AFI is associated with an abnormal 5-minute Apgar score, but there was no association with acidosis or perinatal death in SGA (RR 1.6 [95% CI 0.9–2.6]). Longitudinal studies in early-onset FGR fetuses have shown that the AFI fluid index progressively decreases.¹⁸ One week before acute deterioration, 20%–30% of cases have oligohydramnios.^{18,40} There is limited evidence on the role of oligohydramnios to predict perinatal complications in FGR fetuses managed with Doppler so that its inclusion in management protocols is questionable.

Clinical management of FGR: Follow-up scheme and timing of delivery

No treatment has been demonstrated to be of benefit in growth restriction.^{53–57} Thus, assessment of fetal well-being and timely delivery remain as the main management strategy. The aim behind a clinical protocol for managing FGR is to combine existing evidence on various methods for monitoring fetal well-being in order to establish the risks of fetal injury or death and to balance them against the risks of prematurity if the fetus is delivered.

As we have discussed earlier, the first aim after identifying a “small fetus” is to distinguish between FGR and SGA. Once this distinction is established, from a conceptual

point of view, the concerns of the clinician are to determine (1) whether there is an indication for elective delivery, i.e., whether the risks of leaving the fetus in utero exceed those of delivering electively, and (2) if there is not an indication for elective delivery, when should be the next control scheduled. Although when considered as groups there are clear differences between early-onset and late-onset forms, on an individual basis there is important overlapping of clinical features at borderline gestational ages. In addition, cases with the same gestational age at onset are often detected at different time points during gestation. Consequently, we believe it is most practical to define an integrated protocol for the management of FGR.

As mentioned at the beginning of this chapter, FGR is probably among the obstetrical entities with the greatest variation in clinical practice. We have long stated that FGR must be followed according to a stage-based protocol, which integrates the best available evidence to indicate timing of follow-up and delivery. In our experience, the application of such protocol facilitates clinical management and communication among doctors about what “severity” means and could largely reduce clinical practice variation.

Our suggested approach²⁴ is to group in stages those indices or signs that are associated with similar fetal risks, since they should indicate similar follow-up intervals and timing of delivery. Thus, we suggest to profile several stages, or prognostic groups, which define different management strategies (Table 63.2):

SGA: Excluding infectious and genetic causes, the perinatal results are good. Fortnightly Doppler and growth assessment are standard practice. Labor induction should be recommended at 40 weeks. Fortnightly monitoring is safe.

Table 63.2 Stage-based classification and management of fetal growth restriction

Stage	Pathophysiological correlate	Criteria (any of)	Monitoring ^a	GA/mode of delivery
I	Severe smallness or mild placental insufficiency	EFW <third centile CPR < p5 UA PI > p95 MCA PI < p5 Uterine artery PI > p95	Weekly	37 w LI
II	Severe placental insufficiency	UA AEDV reverse Aol	Biweekly	34 w CS
III	Low-suspicion fetal acidosis	UA REDV DV-PI > p95	1–2 days	30w CS
IV	High-suspicion fetal acidosis	DV reverse atrial flow cCTG <3 ms FHR decelerations	12 hours	26w ^b CS

Note: All Doppler signs described here should be confirmed at least twice, ideally at least 12 hours apart.

Abbreviations: GA, gestational age, LI, labor induction, CS, cesarean section.

^a Recommended intervals in the absence of severe preeclampsia. If FGR is accompanied by this complication, strict fetal monitoring is warranted regardless of the stage.

^b Lower GA threshold recommended according to current literature figures reporting at least 50% intact survival. Threshold could be tailored on parents' wishes or adjusted according to local statistics of intact survival.

Stage I FGR (severe smallness or mild placental insufficiency): Either uterine artery, UA or MCA Doppler, or the CPR is abnormal. In the absence of other abnormalities, evidence suggests a low risk of fetal deterioration before term. Labor induction beyond 37 weeks is acceptable, but the risk of intrapartum fetal distress is increased.⁵¹ Cervical induction with Foley catheter may be recommended to reduce the risk of hyperstimulation. Weekly monitoring seems reasonable.

Stage II FGR (severe placental insufficiency): This stage is defined by UA AEDV or reverse AoI. Despite the evidence for UA AEDV being stronger than that for AoI, observational evidence suggests an association between the latter and abnormal neurodevelopment, so that both criteria are put into a single category. Delivery should be recommended after 34 weeks. The risk of emergent cesarean section at labor induction exceeds 50%, and therefore, elective cesarean section is a reasonable option. Monitoring twice a week is recommended.

Stage III FGR (advanced fetal deterioration, low-suspicion signs of fetal acidosis): The stage is defined by reverse diastolic flow in the UA (REDV) or DV-PI >95th centile. There is an association between a higher risk of stillbirth and poorer neurological outcome. However, since signs suggesting a very high risk of stillbirth within days are not present yet, it seems reasonable to delay elective delivery to reduce as possible the effects of severe prematurity. We suggest delivery should be recommended by

cesarean section after 30 weeks. Monitoring every 24–48 is recommended.

Stage IV FGR (high suspicion of fetal acidosis and high risk of fetal death): There are spontaneous FHR decelerations, reduced short-term variability (<3 ms) in the cCTG, or reverse atrial flow in the DV Doppler. Spontaneous FHR deceleration is an ominous sign, normally preceded by the other two signs, and thus it is rarely observed, but if persistent it may justify emergency cesarean section. cCTG and DV are associated with very high risks of stillbirth within the next 3–7 days and disability. Deliver after 26 weeks by cesarean section at a tertiary care center under steroid treatment for lung maturation. Intact survival exceeds 50% only after 26–28 weeks, and before this threshold, parents should be counseled by multidisciplinary teams. Monitoring every 12–24 hours until is recommended.

Particularly at early gestational ages, and at whatever stage, coexistence of severe PE may distort the natural history, and strict fetal monitoring is warranted since fetal deterioration may occur unexpectedly at any time.

This management protocol is adjusted to available evidence at the time of writing this chapter. Obviously, as new evidence becomes available, any protocol should be adapted accordingly. However, this should not affect the main philosophy of structuring FGR in severity stages that determine the frequency of follow-up and the decision to wait versus deliver electively.

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