NIH Consensus Development Conference

Diagnosing Gestational Diabetes Mellitus

Program and Abstracts

October 29–31, 2012

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Sponsors

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH
Office of Disease Prevention, NIH

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The Agency for Healthcare Research and Quality provided additional conference development support.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

About the Program

The National Institutes of Health (NIH) Consensus Development Program has been organizing major conferences since 1977. The Program generates evidence-based consensus statements addressing controversial issues important to healthcare providers, policymakers, patients, researchers, and the general public. The NIH Consensus Development Program holds one conference a year. The Program is administered by the Office of Disease Prevention within the NIH Office of the Director. Typically, the conferences have one major NIH Institute or Center sponsor, with multiple cosponsoring agencies.

Topic Selection

NIH Consensus Development Conference topics must satisfy the following criteria:

- Have clinical and broad public health importance—the severity of the problem and the feasibility of interventions are key considerations.
- Be controversial or unresolved and amenable to clarification, or reflect a gap between current knowledge and practice that can be narrowed.
- Have an adequately defined base of scientific information from which to answer conference questions.
- Be of cross-cutting concern to a variety of stakeholders.

Conference Process

Before the conference, a systematic evidence review on the chosen topic is performed by one of the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. This report is provided to the panel members approximately 6 weeks prior to the conference, and posted to the Consensus Development Program website once the conference begins, to serve as a foundation of high-quality evidence upon which the conference will build.

The conferences are held over 2-1/2 days. The first day and a half of the conference consists of plenary sessions, in which invited expert speakers present information, followed by "town hall forums," in which open discussion occurs among the speakers, panelists, and the general public in attendance. The panel then develops its draft statement on the afternoon and evening of the second day, and presents it on the morning of the third day for audience commentary. The panel considers these comments in executive session and may revise its draft accordingly. The conference ends with a press briefing, during which reporters are invited to question the panelists about their findings.

Panelists

Each conference panel comprises 12 to 16 members, who can give balanced, objective, and informed attention to the topic. Panel members:

- Must not be employees of the U.S. Department of Health and Human Services.
- Must not hold financial or career (research) interests in the conference topic.
- May be knowledgeable about the general topic under consideration, but must not have published on or have a publicly stated opinion on the topic.
- Represent a variety of perspectives, to include:
  - Practicing and academic health professionals
  - Biostatisticians and epidemiologists
  - Clinical trialists and researchers
  - Nonhealth professionals with expertise in fields relevant to the specific topic (ethicists, economists, attorneys, etc.)
  - Individuals representing public-centered values and concerns

In addition, the panel as a whole should appropriately reflect racial and ethnic diversity. Panel members are not paid a fee or honorarium for their efforts. They are, however, reimbursed

for travel expenses related to their participation in the conference.

Speakers

The conferences typically feature approximately 21 speakers: 3 present the information found in the Evidence-based Practice Center's systematic review of the literature; the other 18 are experts in the topic at hand, have likely published on the topic, and may have strong opinions or beliefs on the topic. Where multiple viewpoints on a topic exist, every effort is made to include speakers who address all sides of the issue.

Conference Statements

The panel's draft report is released online late in the conference's third and final day. The final report is released approximately 6 weeks later. During the intervening period, the panel may edit its statement for clarity and correct any factual errors that might be discovered. No substantive changes to the panel's findings are made during this period.

Each Consensus Development Conference Statement reflects an independent panel's assessment of the medical knowledge available at the time the statement is written; as such, it provides a "snapshot in time" of the state of knowledge on the conference topic. It is not a policy statement of the NIH or the Federal Government.

Dissemination

Consensus Development Conference Statements have robust dissemination:

- A press briefing is held on the last day of the conference to assist journalists in preparing news stories on the conference findings.
- The statement is published online at **http://prevention.nih.gov/gdm.**
- Print copies are mailed and emailed to a wide variety of targeted audiences and are available at no charge through a clearinghouse.
- The conference statement is published in a major peer-reviewed journal.

Contact Us

For conference schedules, past statements, and evidence reports, please contact us:

NIH Consensus Development Program
Information Center
P.O. Box 2577
Kensington, MD 20891

888–NIH–CONSENSUS (888–644–2667)
http://prevention.nih.gov/cdp

Upcoming Conferences

NIH Office of Disease Prevention
Evidence-based Methodology Workshop on Polycystic Ovary Syndrome
December 3–5, 2012

For more information about this conference and other events and resources, please visit **http://prevention.nih.gov.** To join the Office of Disease Prevention mailing list, visit **http://prevention-nih.org/subscribe.**

Recent Conferences

NIH State-of-the-Science Conference:	**Role of Active Surveillance in the Management of Men With Localized Prostate Cancer** *December 5–7, 2011*
NIH Consensus Development Conference:	**Inhaled Nitric Oxide Therapy for Premature Infants** *October 27–29, 2010*
NIH State-of-the-Science Conference:	**Preventing Alzheimer's Disease and Cognitive Decline** *April 26–28, 2010*
NIH Consensus Development Conference:	**Vaginal Birth After Cesarean: New Insights** *March 8–10, 2010*
NIH Consensus Development Conference:	**Lactose Intolerance and Health** *February 22–24, 2010*
NIH State-of-the-Science Conference:	**Enhancing Use and Quality of Colorectal Cancer Screening** *February 2–4, 2010*
NIH Consensus Development Conference:	**Management of Hepatitis B** *October 20–22, 2008*
NIH Consensus Development Conference:	**Hydroxyurea Treatment for Sickle Cell Disease** *February 25–27, 2008*

To access previous conference statements, webcasts, evidence reports, and other conference materials, please visit **http://prevention.nih.gov/cdp.**

General Information

Financial Disclosures

The National Institutes of Health, Centers for Disease Control and Prevention, our planners, and our presenters wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, with the exception of the following:

Name	Company	Financial Relationship
Robert Silver, M.D.	Sera Prognostics	Honorarium, Consultant
Edmond A. Ryan, M.D.	Pfizer	Support for Research Study–One Center of Multicenter Study
	Medtronic	Support for Research Study–Investigator-Initiated Single Center Study
	NovoNordisk	Support for Research Study–One Center of Multicenter Study
Mark A. Espeland, Ph.D., FASA, FSCT	Takeda Global Research	Consultant Fees–Advisory Panel
	Zinfandel Pharmaceuticals	Consultant Fees–Advisory Panel
All other planners and presenters signed statements that they have no financial or other conflicts of interest.		

There is no commercial support for this activity. Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use.

Policy on Panel Disclosure

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

Videocast

Live and archived videocasts may be accessed at **http://videocast.nih.gov.** Archived videocasts will be available approximately 1 week after the conference.

Dining

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:00 p.m., in Building 38A, Level B1, across the street from the main entrance to the Natcher Conference Center.

Online Content

All materials issuing from the NIH Consensus Development Program are available at **http://prevention.nih.gov/cdp.** In addition, remote participants will have the opportunity to provide comments on the panel statement by visiting **http://prevention.nih.gov/cdp/comments** from 8:30 a.m. to 11:30 a.m. on Wednesday, October 31, 2012.

Contents

VI. Given all of the above, what diagnostic approach(es) for gestational diabetes mellitus should be recommended, if any?

Background

Gestational diabetes mellitus (GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy (especially during the third trimester of pregnancy). It is defined as carbohydrate intolerance, which is the inability of the body to adequately process carbohydrates (sugars and starches) into energy for the body, that develops or is first recognized during pregnancy. GDM is estimated to occur in 1% to 14% of U.S. pregnancies, affecting more than 200,000 women annually. It is one of the most common disorders in pregnancy and is associated with an increased risk of complications for the mother and child. Potential complications during pregnancy and delivery include preeclampsia (high blood pressure and excess protein in the urine), cesarean delivery, macrosomia (large birth weight), shoulder dystocia (when a baby's shoulders become lodged during delivery), and birth injuries. For the neonate, complications include difficulty breathing at birth, hypoglycemia (low blood sugar), and jaundice. Up to one-half of women who have GDM during pregnancy will develop type 2 diabetes later in life.

Although the U.S. Preventive Services Task Force found in 2008 that the evidence was insufficient to assess the balance between the benefits and harms of screening women for GDM, the American College of Obstetricians and Gynecologists recommends universal screening for gestational diabetes using patient history, risk factors, or laboratory testing, such as with a glucose challenge test. Different approaches are used internationally for screening and diagnosis of GDM. The standard method in the United States begins with a glucose challenge test, which involves drinking a sweetened liquid containing 50 grams of sugar (glucose). A blood sample is taken after 1 hour, which measures the glucose level. If high, a diagnostic test is administered using a larger dose of glucose, and several blood tests are performed over 3 hours. Depending on the test used, and the chosen blood glucose levels that are used to diagnose GDM, the number of women who will receive the diagnosis will vary. Debate continues regarding the choice of tests and the effectiveness of treatment, especially in women with mild to moderate glucose intolerance. Potential harms of screening for GDM include anxiety for patients and the potentially adverse effects of a high-risk label in pregnancy. In addition, women diagnosed with GDM face stressors including dietary constraints, a need to add or increase exercise, frequent self-monitoring of blood glucose levels, and for some, self-administration of insulin, which will require adjustments of insulin doses.

To better understand the benefits and risks of various GDM screening and diagnostic approaches, the National Institutes of Health has engaged in a rigorous assessment of the available scientific evidence. This process is sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the Office of Disease Prevention. A multidisciplinary planning committee developed the following key questions:

- What are the current screening and diagnostic approaches for gestational diabetes mellitus, what are the glycemic thresholds for each approach, and how were these thresholds chosen?

- What are the effects of various gestational diabetes mellitus screening/diagnostic approaches for patients, providers, and U.S. healthcare systems?

- In the absence of treatment, how do health outcomes of mothers who meet various criteria for gestational diabetes mellitus and their offspring compare with those who do not?

- Does treatment modify the health outcomes of mothers who meet various criteria for gestational diabetes mellitus and their offspring?

- What are the harms of treating gestational diabetes mellitus, and do they vary by diagnostic approach?

- Given all of the above, what diagnostic approach(es) for gestational diabetes mellitus should be recommended, if any?

- What are the key research gaps in the diagnostic approach of gestational diabetes mellitus?

An evidence report on GDM will be prepared through the Agency for Healthcare Research and Quality's Evidence-based Practice Centers program, and a Consensus Development Conference will be held on October 29–31, 2012.

During the conference, invited experts, including the authors of the evidence report, will present scientific data. Attendees will have opportunities to ask questions and provide comments during open discussion periods. After weighing the evidence, an unbiased, independent panel will prepare and present a consensus statement addressing the key conference questions. The statement will be widely disseminated to practitioners, policymakers, patients, researchers, the general public, and the media.

An Explanation of the Scope and Focus of This Conference

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance with onset or identification during pregnancy. Estimated to occur in approximately 7% of U.S. pregnancies, the economic burden of GDM treatment is at least $636 million annually. GDM is one of the most common disorders in pregnancy and is associated with an increased risk of complications for the mother and child, including preeclampsia, cesarean delivery, fetal macrosomia, shoulder dystocia, birth injury, neonatal hyperbilirubinemia, hypoglycemia, and respiratory distress syndrome. Women with a history of GDM have an increased risk of developing type 2 diabetes later in life.

There are a number of controversies regarding GDM in current U.S. practice, including the value of routine screening, the most appropriate method and glycemic thresholds for diagnosis, and the effects of treatment on short- and long-term outcomes in women and children. The National Institutes of Health Consensus Development Program is designed to address controversial questions of public health importance where there is a disconnect between the available data and practice. Consensus Development Conferences address targeted, carefully defined questions with a thorough evidence review and presentations from subject matter experts. An objective panel writes a Consensus Development Conference Statement addressing the conference questions.

Addressing every dilemma surrounding GDM in a single Consensus Development Conference is not feasible. **This conference will focus on issues in making the diagnosis of gestational diabetes,** not on the merits of routine screening or on issues of treatment modalities and their effects. There will be some discussion on screening as it relates to the diagnosis, because in some situations a screening test is part of the diagnostic process; however, this conference is not intended to make a conclusion on the merits of universal screening. Similarly, the issue of treatment will be discussed only as it relates to whether intervening for the condition (as diagnosed) is of benefit.

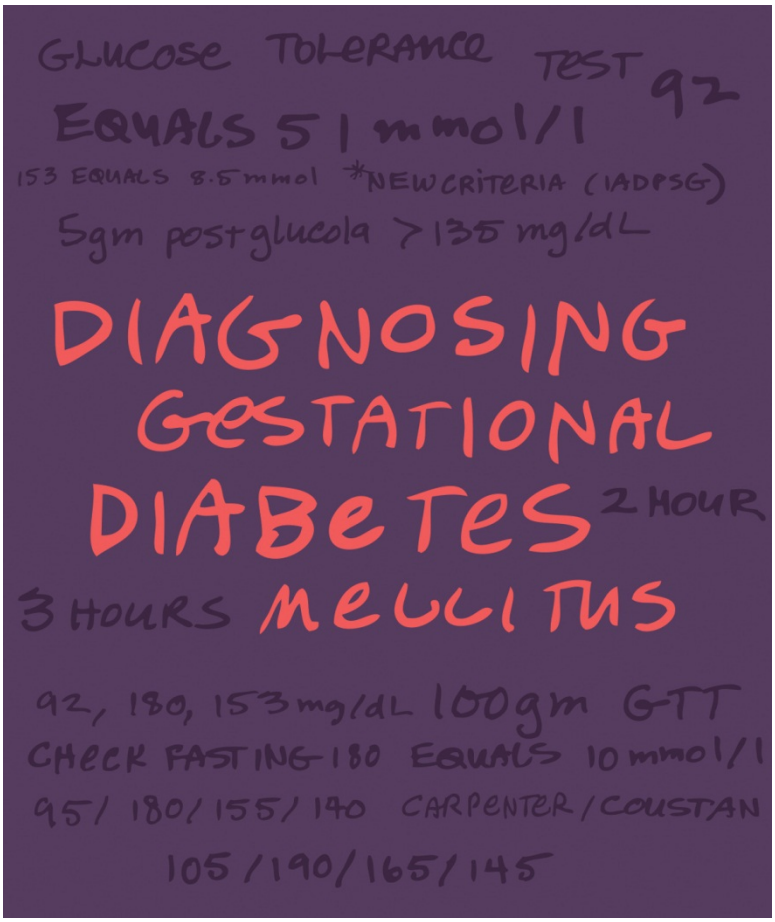
Some questions surrounding GDM have been addressed by other deliberative panels. For example, the U.S. Preventive Services Task Force (USPSTF) has examined the issue of routine screening for GDM. In its 2008 report, the USPSTF determined that “the current evidence is insufficient to assess the balance between the benefits and harms of screening women for GDM either before or after 24 weeks gestation.” In spite of this conclusion, screening for GDM is essentially universal in current U.S. obstetric practice. The USPSTF has begun the process to reexamine the issue of screening. As part of its deliberative process, the USPSTF incorporated questions relevant to its discussions on screening into the Agency for Healthcare Research and Quality (AHRQ) evidence-based report that is also being used for this Consensus Development Conference. Results from this conference will be included in the USPSTF’s evidence review and may inform its conclusions.

In combination, the AHRQ evidence report, the material presented at this conference, and the independent statements and conclusions from both the conference panel and USPSTF will clarify key controversies in GDM.

About the Artwork

The illustration depicts the difficulty that pregnant women and their healthcare providers face when navigating the complexity of screening, diagnosis, and management of gestational diabetes mellitus (GDM). The background handwriting conveys the variety of screening tests available and diagnostic criteria, and reflects the tedious self-monitoring that is required of women diagnosed with GDM. The text also highlights how women diagnosed with GDM must test their glucose levels frequently and record their results, as well as what they have eaten, in a log book. The goal of monitoring is to keep blood sugar levels as close to normal as possible, as this will also help to lower the chances of the fetus developing complications such as large birth weight, shoulder dystocia, and birth injuries. For the neonate, complications can include difficulty breathing at birth, low blood sugar, and jaundice.

The image was conceived and created by the National Institutes of Health's Division of Medical Arts and is in the public domain. No permission is required to use the image. Please credit "William Bramlett/NIH Medical Arts."



Agenda

Monday, October 29, 2012

8:30 a.m. Opening Remarks
Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

8:40 a.m. Charge to the Panel
David M. Murray, Ph.D.
Associate Director for Prevention and Director
Office of Disease Prevention
Office of the Director
National Institutes of Health

8:50 a.m. Conference Overview and Panel Activities
James Peter VanDorsten, M.D.
Panel and Conference Chairperson
Lawrence L. Hester, Jr. Professor
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Medical University of South Carolina

General Overview

9:00 a.m. Overview of Topic
Catherine Y. Spong, *M.D.*
Chief
Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

9:20 a.m. Epidemiology of Gestational Diabetes Mellitus
William M. Callaghan, *M.D., M.P.H.*
Chief
Maternal and Infant Health Branch
Division of Reproductive Health
National Center for Chronic Disease Prevention and Health Promotion
Centers for Disease Control and Prevention

I. What are the current screening and diagnostic approaches for gestational diabetes mellitus, what are the glycemic thresholds for each approach, and how were these thresholds chosen?

9:40 a.m. Current Diagnostic Methods and Thresholds of Gestational Diabetes Mellitus

Donald R. Coustan, M.D.
Professor of Obstetrics and Gynecology
Warren Alpert Medical School of Brown University
Division of Maternal-Fetal Medicine
Women & Infants Hospital of Rhode Island

II. What are the effects of various gestational diabetes mellitus screening/diagnostic approaches for patients, providers, and U.S. healthcare systems?

10:00 a.m. Comparative Benefits and Harms of Varying Diagnostic Thresholds of Gestational Diabetes Mellitus

Wanda Nicholson, M.D., M.P.H., M.B.A.
Director
Diabetes and Obesity Core
Center for Women's Health Research
Associate Professor
Department of Obstetrics and Gynecology
The University of North Carolina School of Medicine

10:20 a.m. **Discussion**

Participants with questions or comments for the speakers should proceed to the designated microphones and wait to be recognized by the panel chairperson. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted on the computers in the registration area. Please be aware that all statements made at the microphone or submitted later are in the public domain.

III. In the absence of treatment, how do health outcomes of mothers who meet various criteria for gestational diabetes mellitus and their offspring compare with those who do not?

10:40 a.m. Evidence-based Practice Center Presentation I: Relative Hyperglycemia and Health Outcomes for the Mother and the Fetus
Lois E. Donovan, M.D., FRCPC
Clinical Associate Professor and Medical Director
Diabetes in Pregnancy
Division of Endocrinology and Metabolism
Department of Obstetrics and Gynecology
University of Calgary
Alberta Health Services

Lisa Hartling, Ph.D.
Assistant Professor
Department of Pediatrics
Director
University of Alberta Evidence-based Practice Centre
Alberta Research Centre for Health Evidence
University of Alberta

11:00 a.m. Relative Hyperglycemia and Health Outcomes for the Mother
Patrick M. Catalano, M.D.
Professor
Reproductive Biology
Director
Center for Reproductive Health
MetroHealth Medical Center
Case Western Reserve University

11:20 a.m. Relative Hyperglycemia and Health Outcomes for the Fetus
David J. Pettitt, *M.D.*
Senior Scientist
Sansum Diabetes Research Institute

11:40 a.m. **Discussion**

12:10 p.m. **Lunch—Panel Executive Session**

IV. Does treatment modify the health outcomes of mothers who meet various criteria for gestational diabetes mellitus and their offspring?

1:30 p.m. Evidence-based Practice Center Presentation II: Benefits of Treatment of Gestational Diabetes Mellitus on Maternal and Fetal Health Outcomes

Lois E. Donovan, M.D., FRCPC
Clinical Associate Professor and Medical Director
Diabetes in Pregnancy
Division of Endocrinology and Metabolism
Department of Obstetrics and Gynecology
University of Calgary
Alberta Health Services

Lisa Hartling, Ph.D.
Assistant Professor
Department of Pediatrics
Director
University of Alberta Evidence-based Practice Centre
Alberta Research Centre for Health Evidence
University of Alberta

1:50 p.m. Benefits of Treatment of Gestational Diabetes Mellitus on Maternal Health Outcomes

Mark B. Landon, M.D.
Richard L. Meiling Professor and Chair
Department of Obstetrics and Gynecology
The Ohio State University College of Medicine and
Wexner Medical Center

2:10 p.m. Benefits of Treatment of Gestational Diabetes Mellitus on Fetal/Infant Health Outcomes

Matthew W. Gillman, *M.D., S.M.*
Director
Obesity Prevention Program
Professor
Department of Population Medicine
Harvard Medical School
Harvard Pilgrim Health Care Institute

2:30 p.m. **Discussion**

V. What are the harms of treating gestational diabetes mellitus, and do they vary by diagnostic approach?

3:00 p.m. Evidence-based Practice Center Presentation III: Harms of Treatment of Gestational Diabetes Mellitus and Relationship to Diagnostic Threshold

Lois E. Donovan, M.D., FRCPC
Clinical Associate Professor and Medical Director
Diabetes in Pregnancy
Division of Endocrinology and Metabolism
Department of Obstetrics and Gynecology
University of Calgary
Alberta Health Services

Lisa Hartling, Ph.D.
Assistant Professor
Department of Pediatrics
Director
University of Alberta Evidence-based Practice Centre
Alberta Research Centre for Health Evidence
University of Alberta

3:20 p.m. Harms of Treatment of Gestational Diabetes Mellitus and Relationship to Diagnostic Threshold

Timothy Cundy, M.D.
Professor of Medicine
Faculty of Medical and Health Sciences
The University of Auckland

3:40 p.m. Economic Implications of Altering Gestational Diabetes Mellitus Diagnostic Criteria

Aaron B. Caughey, *M.D., Ph.D., M.P.P., M.P.H.*
Professor and Chair
Department of Obstetrics and Gynecology
Julie Neupert Stott Director
Center for Women's Health
Oregon Health & Science University

4:00 p.m. Practice Implications of Altering Gestational Diabetes Mellitus Diagnostic Criteria

William H. Barth, Jr., *M.D.*
Chief
Division of Maternal Fetal Medicine
Obstetrics and Gynecology Service
Massachusetts General Hospital
Associate Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School

Monday, October 29, 2012 ***(continued)***

V. What are the harms of treating gestational diabetes mellitus, and do they vary by diagnostic approach? ***(continued)***

4:20 p.m. **Discussion**

5:00 p.m. **Adjournment**

Tuesday, October 30, 2012

VI. Given all of the above, what diagnostic approach(es) for gestational diabetes mellitus should be recommended, if any?

8:30 a.m. Review of Maternal Experience of Having Diabetes Mellitus in Pregnancy
Susan H. McCrone, *Ph.D., R.N., PMHCNS-BC*
Professor
West Virginia University School of Nursing

8:50 a.m. Pro Status Quo
Brian M. Casey, *M.D.*
Gillette Professorship
Obstetrics and Gynecology
The University of Texas Southwestern Medical Center

9:10 a.m. Pro International Association of Diabetes and Pregnancy Study Groups
Boyd E. Metzger, *M.D.*
Tom D. Spies Professor of Metabolism and Nutrition
Department of Medicine
Division of Endocrinology, Metabolism and Molecular Medicine
Northwestern University
Feinberg School of Medicine

9:30 a.m. Pro Alternative
Edmond A. Ryan, *M.D.*
Professor
Department of Medicine
Division of Endocrinology
University of Alberta

9:50 a.m. **Discussion**

11:00 a.m. **Adjournment**

Wednesday, October 31, 2012

9:00 a.m. **Presentation of the Draft Consensus Statement**
The panel chairperson will read the draft statement to the assembled audience.

9:30 a.m. **Discussion**
The panel chairperson will call for questions and comments from the audience on the draft statement, beginning with the introduction and continuing through each subsequent section, in turn. Please confine your comments to the section under discussion. The chairperson will use discretion in proceeding to subsequent sections so that comments on the entire statement may be heard during the time allotted. Participants with comments should proceed to the designated microphones and wait to be recognized by the panel chairperson. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted on the computers in the registration area. For participants viewing the remote webcast, comments may be submitted online at **http://prevention.nih.gov/cdp/comments.** *Comments will not be accepted after 11:30 a.m. Please be aware that all statements made at the microphone or submitted later are in the public domain.*

11:00 a.m. **Adjournment—Panel Meets in Executive Session**

2:00 p.m. **Press Telebriefing**
The panel will provide a summary of its findings to the press and will answer questions from reporters via telebriefing. Only members of the press are permitted to ask questions of the panel during this time. Interested conference participants who are not members of the press may call in (from a remote location) to listen to the live telebriefing. Please go to **http://prevention.nih.gov/gdm** *for instructions on joining the call.*

The panel's draft statement will be posted to **http://prevention.nih.gov/gdm** *as soon as possible after the close of proceedings, and the final statement will be posted 4 to 6 weeks later.*

Panel

Panel Chairperson: **James Peter VanDorsten, M.D.**
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Abstracts

The abstracts are designed to inform the panel and conference participants, as well as to serve as a reference document for any other interested parties. We would like to thank the speakers for preparing and presenting their findings on this important topic.

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Please note that where multiple authors are listed in an abstract, the underline denotes the presenting author(s).

Epidemiology of Gestational Diabetes Mellitus

William M. Callaghan, M.D., M.P.H.

Gestational diabetes mellitus (GDM) is the condition of carbohydrate intolerance of varying severity that begins or is first recognized during pregnancy.[1] For some, GDM is really type 2 diabetes not previously diagnosed, but for most, the glucose intolerance subsides after delivery. The diagnostic criteria used to diagnose GDM vary by providers, influencing the prevalence of GDM. The prevalence also varies significantly among different populations and ethnicities. Hence, discussion of the epidemiology of GDM must consider the degree of homogeneity or heterogeneity of the population with regard to race and ethnicity, body composition, age, and changes in screening and diagnostic criteria.

The classic study by O'Sullivan and Mahan established the original cut-points for the 3-hour glucose tolerance test in pregnancy not based on the risks associated with hyperglycemia during pregnancy, but on risk of developing diabetes later in life.[2] Although changes in cut-points have been implemented since the original work of O'Sullivan and Mahan,[3,4] it is only recently that diagnostic criteria have been linked to maternal and neonatal outcomes.[5]

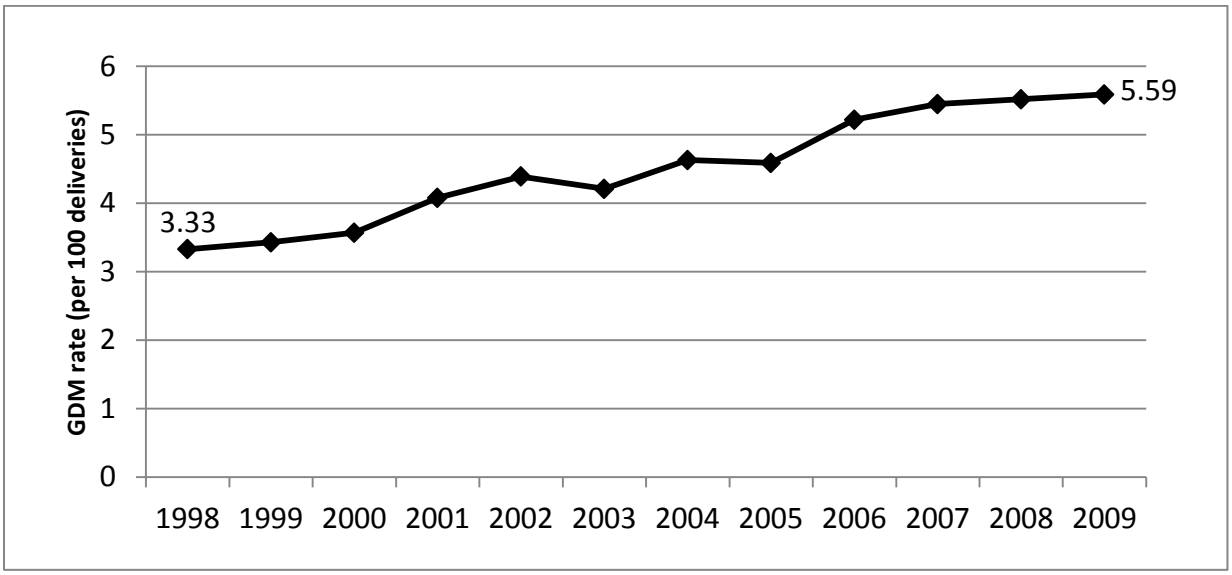
There are potentially two sources of data for determining national estimates of the prevalence of GDM in the United States: vital statistics and administrative hospital discharge data. The 2003 revision of the U.S. Standard Certificate of Live Birth has a field asking specifically about the presence of GDM, and as of 2008, 27 states had adopted the 2003 revision. In 2008, there were 4.1 cases of GDM per 100 live births reported on the birth certificates. However, this represents a limited reporting area and hence may not be generalizable to the country as a whole, because births in these 27 states may not be representative of births in the entire country.[6] Moreover, birth certificates lack sensitivity for estimating the prevalence of maternal conditions.[7] Therefore, although the universal adoption of the 2003 revised U.S. Standard Certificate of Live Birth may be useful for monitoring change in GDM prevalence over time, simply adopting the certificate will not correct the problem of underestimation of the true prevalence.

The Healthcare Cost and Utilization Project Nationwide Inpatient Sample is a nationally representative sample of inpatient care.[8] Since all women with GDM who can be diagnosed will have been diagnosed by their delivery hospitalization, the prevalence of GDM in the United States can be estimated by examining the International Classification of Diseases–9th Revision code 648.8x (abnormal glucose tolerance) among women who deliver. A similar strategy over time can be used to monitor trends. In 2009, there were 5.6 cases of GDM per 100 deliveries, representing a significant increase from 1998 when there were 3.3 cases per 100 deliveries (p for trend=0.001) (Figure 1). Although hospital discharge data also have been shown to have less than 100% sensitivity for reporting maternal conditions, sensitivity consistently exceeds that of birth certificates.[7]

Neither birth certificates nor hospital discharge data take into consideration the criteria used to make the diagnosis of GDM, and thus trends using either of these sources may be affected by changes in criteria. For example, changing from using National Diabetes Data Group criteria to Carpenter and Coustan criteria was shown in one study of a large health maintenance association to increase the prevalence of GDM by 50%.[9] The degree to which such changes have influenced national population-based trends is unknown. However, multiple studies have shown increases among diverse populations during the decade of the 1990s and early 21st

century regardless of whether GDM was ascertained from birth certificates, administrative data, or clinical databases, suggesting that the observed U.S. trend is real.[10–14] A single study from Southern California observed a stable trend for GDM from 1999 through 2005, while increases were seen in type 2 diabetes.[15] The stability of GDM prevalence in this study may be indicative of an earlier diagnosis (e.g., before pregnancy) of type 2 diabetes among women who would not have otherwise been discovered until their GDM diagnosis.

Figure 1. Rate of Gestational Diabetes Mellitus (per 100 Deliveries), 1998–2009, United States, Nationwide Inpatient Sample



The observed increase in GDM nationally and in smaller populations and selected healthcare settings is consistent with changes in known risk factors for GDM. Advanced maternal age, family history of diabetes, and higher body mass index are well-documented risk factors, and GDM is more common among Asian, Hispanic/Latina, and Native American women.[16,17] Since 1995, births to women age 35 and older have increased by more than 20% and now account for one in seven births.[18] Since 1980, the percentage of people in the United States with diagnosed diabetes has almost tripled; more women of reproductive age have a family member affected with diabetes.[19] Obesity has increased among pregnant women. Pre-pregnancy obesity has increased across all age and race/ethnicity groups,[20] and currently more than 20% of women enter pregnancy obese.[21] A recent analysis calculated a population-attributable fraction of obesity to GDM of 30%, suggesting that if obesity is causal, 30% of all GDM could be prevented if pregnancy obesity could be prevented.[22] The proportion of births to Hispanic women and Asian women has nearly doubled in the past 20 years.[23]

In conclusion, the current best estimate for GDM prevalence in the United States is 5% to 6%, and it has been increasing. The prevalence is affected by the criteria for screening and diagnosis. Risk factors for GDM have increased, and populations at highest risk for GDM constitute an increasing proportion of births. Moreover, groups at highest risk are not distributed evenly throughout the United States; hence, specific state and local burdens of GDM are likely to be greater than the estimates for the United States as a whole. Further increases in GDM rates will depend on changes in screening and diagnostic criteria and changes in risk factor distribution.

References

1. American College of Obstetricians and Gynecologists. Gestational diabetes. ACOG Practice Bulletin No. 30. *Obstet Gynecol.* 2001;98(3):525–538.

2. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes.* 1964;13:278–285.

3. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes.* 1979;28(12):1039–1057.

4. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol.* 1982;144(7):768–773.

5. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991–2002.

6. Osterman MJK, Martin JA, Mathews TJ, et al. Expanded data from the new birth certificate, 2008. *Natl Vital Stat Rep.* 2011;59(7):1–28.

7. Lydon-Rochelle MT, Holt VL, Cárdenas V, et al. The reporting of pre-existing maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. *Am J Obstet Gynecol.* 2005;193(1):125–134.

8. Overview of the Nationwide Inpatient Sample (NIS). HCUP Databases. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; June 2012. Available at: http://hcup-us.ahrq.gov/nisoverview.jsp. Accessed June 1, 2012.

9. Magee MS, Walden CE, Benedetti TJ, et al. Influence of diagnostic criteria on the incidence of gestational diabetes and perinatal morbidity. *JAMA.* 1993;269(5):609–615.

10. Dabelea D, Snell-Bergen JK, Hartsfield CL, et al. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Screening Program. *Diabetes Care.* 2005;28(3):579–584.

11. Moum KR, Holzman GS, Harwell TS, et al. Increasing rate of diabetes in pregnancy among American Indian and white mothers in Montana and North Dakota, 1989–2000. *Matern Child Health J.* 2004;8(2):71–76.

12. Dietz PM, Vesco KK, Callaghan WM, et al. Postpartum screening for diabetes after a gestational diabetes mellitus-affected pregnancy. *Obstet Gynecol.* 2008;112(4):868–874.

13. Thorpe LE, Berger D, Ellis JA, et al. Trends and racial/ethnic disparities in gestational diabetes among pregnant women in New York City, 1990–2001. *Am J Public Health.* 2005;95(9):1536–1539.

14. Ferrara A, Kahn HS, Quesenberry CP, et al. An increase in the incidence of gestational diabetes mellitus: Northern California, 1991–2000. *Obstet Gynecol.* 2004;103(3):526–533.

15. Lawrence JM, Contreras R, Chen W, et al. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. *Diabetes Care.* 2008;31(5):899–904.

16. Ramos GA, Caughey AB. The interrelationship between ethnicity and obesity on obstetric outcomes. *Am J Obstet Gynecol.* 2005;193(3 Pt 2):1089–1093.

17. Solomon CG, Willet WC, Carey VJ, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. *JAMA.* 1997;278(13):1078–1083.

18. Centers for Disease Control and Prevention, National Center for Health Statistics. Natality Information: Live Births. CDC WONDER online database. Available at: http://wonder.cdc.gov/natality.html. Accessed May 31, 2012.

19. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. Crude and age-adjusted percentage of civilian, noninstitutionalized population with diagnosed diabetes, United States, 1980–2010. Diabetes Data and Trends. Available at: http://cdc.gov/diabetes/statistics/prev/national/figage.htm. Accessed May 31, 2012.

20. Kim SY, Dietz PM, England L, et al. Trends in pre-pregnancy obesity in nine states, 1993–2003. *Obesity (Silver Spring).* 2007;15(4):986–992.

21. Chu SY, Kim SY, Bish CL. Prepregnancy obesity prevalence in the United States, 2004–2005. *Matern Child Health J.* 2009;13(5):614–620.

22. Kim SY, England L, Wilson HG, et al. Percentage of gestational diabetes mellitus attributable to overweight and obesity. *Am J Public Health.* 2010;100(6):1047–1052.

23. Martin JA, Hamilton BE, Ventura SJ, et al. Births: final data for 2009. *Natl Vital Stat Rep.* 2011;60(1):1–70.

Current Diagnostic Methods and Thresholds of Gestational Diabetes Mellitus

Donald R. Coustan, M.D.

A number of different diagnostic methods and criteria for gestational diabetes mellitus (GDM) are in use around the world. In the United States, the majority of obstetricians use a 50-gram, 1-hour glucose challenge as a screening test and some variation of the 100-gram, 3-hour oral glucose tolerance test based on the criteria of O'Sullivan and Mahan.[1] In much of the world, the World Health Organization criteria for the 75-gram oral glucose tolerance test are utilized. Fifty-gram challenges also have been adopted. To determine whether adoption of a single set of internationally agreed-upon diagnostic criteria is appropriate, based on pregnancy outcomes, it is important to understand how the current criteria came into being.

In 1882, J. Matthews Duncan noted that diabetes may come on during pregnancy, occur only during pregnancy, and cease with the termination of pregnancy.[2] In 1946, Miller observed that perinatal mortality rates were increased in pregnancies occurring before women developed diabetes.[3] In 1952, Jackson reported a high likelihood of previous stillbirth and macrosomia in women with diabetes,[4] and shortly thereafter Carrington first used the term "gestational diabetes."[5] At that time, the diagnosis of diabetes was based on the U.S. Public Health Service criteria, utilizing a 100-gram, 3-hour oral glucose tolerance test. Diabetes was diagnosed if (1) both the fasting and 3-hour value were ≥130 mg/dL, or (2) one of the two values was ≥130 mg/dL and the 1-hour value was ≥195 mg/dL and the 2-hour value was ≥140 mg/dL.

In 1964, O'Sullivan and Mahan observed that pregnancy changes carbohydrate metabolism and that oral glucose tolerance test results may be altered as a result.[1] They suggested that nonpregnant norms may not be valid during pregnancy. They reported their observations of a 100-gram, 3-hour oral glucose tolerance test on 752 unselected pregnant women in the first (n=20), second (n=339), or third (n=393) trimester. They derived potential thresholds of one, two, and three standard deviations above the mean for each of the four venous blood glucose values (Somogyi-Nelson method of glucose analysis) and applied them retrospectively to a second data set of oral glucose tolerance tests in 1,333 previous pregnancies. The latter women had undergone periodic oral glucose tolerance tests in the nonpregnant state. Two elevated values were required, because O'Sullivan did not want to rely on a single laboratory test to make the diagnosis.

Numerous reports spanning 20 or more years have documented an increase in adverse outcomes when only one oral glucose tolerance test value is elevated.[6,7] Thresholds of two standard deviations above the mean were chosen because they identified 1.9% of gravidas as having GDM, whereas one standard deviation would have identified 16% of the population, a proportion that concerned O'Sullivan because of the potential psychological effect of overdiagnosis. The 2% prevalence of GDM was similar to the 2% prevalence of diabetes in the nonpregnant community.[8] Centers for Disease Control and Prevention data for 2010 suggest that more than 11% of adult Americans currently have diabetes, and an additional 25% have prediabetes.[9] Twenty-two percent of O'Sullivan's women with GDM would have developed diabetes over the subsequent 8 years, and approximately 40% over 20 years.[10] The recommended thresholds are shown in Table 1, both unrounded and rounded to the nearest 5 mg/dL.

Table 1. Various Versions of O'Sullivan 100-Gram, 3-Hour Oral Glucose Tolerance Test Criteria for Gestational Diabetes Mellitus (Two or More Elevated Values Required To Make the Diagnosis)

	O'Sullivan Unrounded* (mg/dL)	O'Sullivan Rounded* (mg/dL)	NDDG† (mg/dL)	Carpenter/Coustan‡ (mg/dL)
Fasting	90	90	105	95
1 hour	165	165	190	180
2 hours	143	145	165	155
3 hours	127	125	145	140

NDDG = National Diabetes Data Group.
*Venous whole blood, Somogyi-Nelson.
†Plasma.
‡Plasma, glucose oxidase, or hexokinase.

In 1978, the American College of Obstetricians and Gynecologists recommended use of either the O'Sullivan criteria or another set of criteria proposed by Mestman.[11] In 1979, the National Diabetes Data Group converted the O'Sullivan criteria to plasma rather than whole blood by multiplying each of the rounded values by 15% (Table 1).[12] Carpenter and Coustan recommended a different set of conversions in 1982[13]; these took into account the change from the less specific Somogyi-Nelson method to specific enzymatic methods, as well as the 14% increase when measuring glucose in plasma rather than whole blood (Table 1). The American College of Obstetricians and Gynecologists endorsed the National Diabetes Data Group conversion in 1986,[14] and in 1989, Sacks demonstrated that the Carpenter and Coustan conversions more faithfully reproduced the original O'Sullivan criteria than did the National Diabetes Data Group conversions.[15] By 1994, the American College of Obstetricians and Gynecologists recommended either of the two conversions.[16] The latter recommendation is still in effect. In 1998, the Fourth International Workshop-Conference on Gestational Diabetes Mellitus recommended the use of the Carpenter and Coustan conversions,[17] and the American Diabetes Association did so shortly thereafter.

Most caregivers in the United States perform a 50-gram, 1-hour oral glucose challenge test, often called the "O'Sullivan screen," to identify women who need the full oral glucose tolerance test. In 1973, O'Sullivan described the screening test in which venous whole blood glucose was measured (Somogyi-Nelson) 1 hour after a 50-gram challenge in 752 unselected pregnant women, all of whom also underwent a 100-gram, 3-hour oral glucose tolerance test. A value ≥130 mg/dL (which would translate to 143 mg/dL if plasma glucose was measured with an enzymatic method) identified 79% of the women with GDM.[18] Subsequently, Carpenter and Coustan suggested that the threshold for further testing be lowered from 143 mg/dL (130 mg/dL whole blood, Somogyi-Nelson) to 135 mg/dL when plasma samples and enzymatic methods of analysis were used.[19] Subsequently, a threshold of 130 mg/dL was demonstrated to have nearly 100% sensitivity, whereas a threshold of 140 mg/dL had 90% sensitivity.[20] The tradeoff would be that 14% of gravidas would require the full oral glucose tolerance test at a threshold of 140 mg/dL, while 23% would require oral glucose tolerance tests at a threshold of 130 mg/dL. The American College of Obstetricians and Gynecologists recommends that either of these

thresholds may be used.[13] The use of historical risk factors as a screening test for GDM has repeatedly been shown to lack sensitivity.[21]

Although one or the other variation of the O'Sullivan criteria is universally used in the United States, this is not the case in the rest of the world. The World Health Organization recommends the use of a 75-gram, 2-hour oral glucose tolerance test. GDM is diagnosed if the 2-hour plasma glucose value is ≥140 mg/dL, which is the criterion used to diagnose impaired glucose tolerance in the nonpregnant state.[22] The Australasian Diabetes in Pregnancy Society recommends the use of a 75-gram, 2-hour oral glucose tolerance test. A fasting plasma glucose ≥5.5 mmol/L (99 mg/dL) and/or a 2-hour value ≥8.0 mmol/L (144 mg/dL) is used to make the diagnosis. These diagnostic criteria were established by consensus.[23] Both the World Health Organization and the Australasian Diabetes in Pregnancy Society require only a single elevated value to make the diagnosis of GDM. Neither the O'Sullivan criteria, nor the World Health Organization or Australasian Diabetes in Pregnancy Society criteria, are based on pregnancy outcome.

In summary, the current approach in the United States includes a two-step sequence of screening and diagnostic testing. Diagnostic criteria commonly used in this country require two abnormal values on a 3-hour, 100-gram oral glucose tolerance test and are based upon two standard deviations above the mean. Values used in other countries are either the same values as in nonpregnant individuals or are based upon the opinions of experts. None of the current criteria are evidence based upon outcomes of pregnancy, and numerous different strategies are in use. It is impossible to compare prevalence or treatment results among countries and, to a great extent, even within our own country.

References

1. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes*. 1964;13:278–285.

2. Duncan JM. On puerperal diabetes. *Trans Obstet Soc London*. 1882;24:256–285.

3. Miller HC. The effect of diabetic and prediabetic pregnancies on the fetus and newborn infant. *J Pediatr.* 1946;29(4):455–461.

4. Jackson WP. Studies in pre-diabetes. *Br Med J.* 1952;2(4786):690–696.

5. Carrington ER, Shuman CR, Reardon HS. Evaluation of the prediabetic state during pregnancy. *Obstet Gynecol.* 1957;9(6):664–669.

6. Langer O, Anyaegbunam A, Brustman L, et al. Management of women with one abnormal oral glucose tolerance test value reduces adverse outcome in pregnancy. *Am J Obstet Gynecol*. 1989;161(3):593–599.

7. Landon MB, Mele L, Spong CY, et al.; *Eunice Kennedy Shriver* National Institute of Child Health, and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. The relationship between maternal glycemia and perinatal outcome. *Obstet Gynecol.* 2011;117(2 Pt 1):218–224.

8. Wilkerson HL, Krall LP. Diabetes in a New England town; a study of 3,516 persons in Oxford, Mass. *JAMA.* 1947;135(4):209–216.

9. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011. Available at: http://cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed June 2, 2012.

10. O'Sullivan JB. Subsequent morbidity among gestational diabetic women. In Sutherland HW, Stowers JM, eds. Carbohydrate Metabolism in Pregnancy and the Newborn: Incorporating the Proceedings of the International Colloquium at Abderdeen, Scotland, April 1983. New York: Churchill Livingstone; 1984:174–180.

11. Mestman JH, Anderson GV, Barton P. Carbohydrate metabolism in pregnancy. A study of 658 patients with the use of the oral glucose tolerance test and the predinisolone glucose tolerance test. *Am J Obstet Gynecol.* 1971;109(1):41–45.

12. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes.* 1979;28(12):1039–1057.

13. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol.* 1982;144(7):768–773.

14. American College of Obstetricians and Gynecologists. Management of diabetes mellitus in pregnancy. *ACOG Technical Bulletin* #92. Washington DC: ACOG; 1986.

15. Sacks DA, Abu-Fadil S, Greenspoon JS, et al. Do the current standards for glucose tolerance testing in pregnancy represent a valid conversion of O'Sullivan's original criteria? *Am J Obstet Gynecol.* 1989;161(3):638–641.

16. American College of Obstetricians and Gynecologists. Diabetes and pregnancy. *ACOG Technical Bulletin* #200. Washington DC: ACOG; 1994.

17. Metzger BE, Coustan DR; The Organizing Committee. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care.* 1998;21(Suppl 2):B161–B167.

18. O'Sullivan JB, Mahan CM, Charles D, et al. Screening criteria for high-risk gestational diabetic patients. *Am J Obstet Gynecol.* 1973;116(7):895–900.

19. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol.* 1982;144(7):768–773.

20. Coustan DR, Nelson C, Carpenter MW, et al. Maternal age and screening for gestational diabetes: a population-based study. *Obstet Gynecol.* 1989;73(4):557–561.

21. Östlund I, Hanson U. Occurrence of gestational diabetes mellitus and the value of different screening indicators for the oral glucose tolerance test. *Acta Obstet Gynecol Scand*. 2003;82(2):103–108.

22. World Health Organization. About Diabetes. 2012. Available at: who.int/diabetes/action_online/basics/en/index1.html. Accessed May 31, 2012.

23. Hoffman L, Nolan C, Wilson JD, et al. Gestational diabetes mellitus—management guidelines. The Australasian Diabetes in Pregnancy Society. *Med J Aust.* 1998;169(2):93–97.

Comparative Benefits and Harms of Varying Diagnostic Thresholds of Gestational Diabetes Mellitus

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Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance of variable degree with onset or first recognition during pregnancy, is the most common medical condition of pregnancy.[1] The prevalence of GDM has increased with the prevalence of obesity in the United States. GDM affects approximately 240,000 (6%–7%) of the more than 4 million births occurring annually in the United States and is associated with several maternal and infant complications.[2,3] Worldwide, the two primary screening/diagnostic strategies for GDM are the sequential or two-step strategy (initial 50-gram, 1-hour glucose challenge test followed by, in those who test positive, a 100-gram, 3-hour glucose tolerance test using either the Carpenter-Coustan or National Diabetes Data Group cutoff values) and the 75-gram, 2-hour glucose tolerance test strategy often referred to as the one-step strategy.[1] The majority of providers in the United States practice universal screening in which all pregnant women undergo testing between the 24th and 28th week of pregnancy using the two-step process.[4]

Advantages of the two-step strategy are the ability to broadly screen women with a shorter test, with fewer women subjected to a longer test. Screening with the glucose challenge test requires women to take less time away from work or home. Moreover, the shorter glucose challenge test can be administered efficiently in diverse clinical settings, including private offices, healthcare departments, and hospital-based clinics where women receive prenatal care. Disadvantages include the need for women to return for the 3-hour oral glucose tolerance test to confirm the diagnosis. In contrast, the advantage of the one-step strategy is that the diagnosis of GDM is made with completion of a single test. Also, the one-step strategy provides consistency with the approach used in other countries with national screening programs. A disadvantage is that all women are required to present in the fasting state, whereas the glucose challenge test does not require women to be fasting. The 75-gram oral glucose tolerance test may be difficult for women who use public transportation, because it requires early morning testing.

Diagnostic criteria for GDM have garnered increasing attention since publication of the findings of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.[5] The HAPO study, an international observational study of approximately 25,000 women undergoing a 75-gram oral glucose tolerance test, demonstrated that maternal hyperglycemia at levels below those diagnostic for GDM were associated with specific adverse outcomes for mothers and their infants. There were continuous graded relationships between higher maternal glucose and each of the primary outcomes: birth weight >90th percentile for gestational age, primary cesarean delivery, cord blood C-peptide >90th percentile, and clinically defined neonatal hypoglycemia.[5] In view of this emerging evidence that even mild maternal hyperglycemia is associated with perinatal risks, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) debated new criteria for the diagnosis of GDM and overt diabetes in pregnancy.[6]

The IADPSG Consensus Panel considered several diagnostic thresholds for GDM based on the average glucose values at which the odds for each of the primary outcomes indicated above was 1.5, 1.75, or 2.0 times the estimated odds of these outcomes at mean glucose values from the HAPO data. As shown in Table 1, the proportion of the cohort with fasting plasma glucose levels equal to or greater than thresholds at each adjusted odds ratio differed substantially. Current IADPSG criteria include (1) use of the 75-gram oral glucose tolerance test with the

following threshold values for fasting plasma glucose, 1-hour, and 1-hour oral glucose tolerance test plasma glucose concentrations (92, 180, 153 mg/dL, respectively); and (2) diagnosis of GDM if one or more thresholds is exceeded. The lower diagnostic thresholds coupled with a diagnosis based on a single blood glucose measurement differ substantially from the established Carpenter-Coustan and National Diabetes Data Group criteria, which have higher thresholds and diagnosis based on two or more abnormal values. Applying the IADPSG criteria increases the prevalence of GDM to 17.8%—a two- to threefold increase in the number of women diagnosed with GDM compared with the Carpenter-Coustan and National Diabetes Data Group criteria.

Table 1. Fasting Plasma Glucose Thresholds of Women With Gestational Diabetes Mellitus at Each Adjusted Odds Ratio

Glucose Concentration Threshold			
Adjusted Odds Ratio	**mmol/L**	**mg/dL**	**Percentage Above Threshold***
1.5	5.0	90	12
1.75	5.1	92	8
2.0	5.3	95	4

*Represents percentage of women in Hyperglycemia and Adverse Pregnancy Outcome study above threshold value.

Consideration of the IADPSG, Carpenter-Coustan, and National Diabetes Data Group criteria has fostered debate because of the potential effects of various diagnostic approaches for multiple stakeholders—patients, providers, and the healthcare system. The potential benefits of detecting and treating mild GDM are substantial and include a reduction in fetal size, metabolic alterations that may predispose the infant to accelerated early growth, and a reduction in the cesarean delivery rate.[5]

There are harms associated with the various diagnostic thresholds. IADPSG criteria may have a higher sensitivity but lower specificity (i.e., more false-positive tests) than the two-step process (50 grams/Carpenter-Coustan/National Diabetes Data Group). Positive results are more common with the IADPSG criteria. Therefore, the likelihood of overdiagnosis of GDM, with downstream consequences of unnecessary testing and treatments (i.e., medications, labor induction, cesarean delivery), may increase with strategies that use lower thresholds.[7] It is difficult to estimate the precise magnitude of overdiagnosis associated with any screening or treatment strategy, but it is of concern since it leads to unnecessary surveillance, diagnostic tests, and treatments with harms and no potential benefit. Abnormal screening test results may be associated with short psychological harms (2–3 weeks) as shown with treatment for GDM.[8] Also, a substantially higher number of women will be required to undergo daily glucose testing (i.e., fingersticks) and additional prenatal care visits. Women also may undergo unnecessary additional testing, including nonstress tests and multiple ultrasounds, or overtreatment with oral medications or insulin.

It also is critical to evaluate objectively how the twofold increase in GDM will impact the ability of providers to care for their patients, and the downstream consequences for providers and the

healthcare system. Providing nutritional counseling, diabetic teaching, and self-glucose monitoring may improve glucose control and perinatal outcomes, but will require an increase in staff time, and possibly additional staff, to accommodate the increased demand for teaching.[7] Adjustment of provider appointment schedules also may be required to accommodate additional antenatal visits. Additional challenges include limited phlebotomy space to accommodate the large number of women presenting for the 2-hour oral glucose tolerance test. With the IADSPG approach, all women would be required to present in the morning after an overnight fast, which could lead to overcrowding, particularly in private office and health department settings where there are fewer phlebotomy staff.

A benefit of screening/diagnosis of GDM is the ability to identify women who may be at risk for developing type 2 diabetes and to provide postpartum glucose testing.[9] Current rates of postpartum screening among women with a history of GDM are low; only half of women in most populations, regardless of race/ethnicity and socioeconomic strata, are screened.[10] Further studies to identify barriers and facilitators of adherence to postpartum screening, from the perspective of women and their providers,[11] are needed to inform the development of effective, practice-based interventions to improve compliance with postpartum screening, regardless of the strategy used for diagnosis.

Evaluation of the economic impact of varying diagnostic thresholds for the diagnosis of GDM is incomplete. Early studies suggested that a decrease in adverse perinatal outcomes offset the costs of screening and treatment. One cost-effectiveness analysis comparing the two-step method (50-gram/100-gram oral glucose tolerance test) method with the 75-gram oral glucose tolerance test using the IADPSG criteria suggests that the cost of the two-step method is lower than that of the one-step, 75-gram oral glucose tolerance test,[12] which is consistent with earlier studies.[13,14] Another analysis[15] reported that the IADPSG guidelines for the 2-hour oral glucose tolerance test is more costly, but the method is cost effective if treatment costs are well contained. The model was moderately sensitive to treatment costs (e.g., supplies, materials, procedures, testing) and reductions in preeclampsia and cesarean delivery rates.[15] Further information on treatment efficacy and reliable cost estimates will inform future analyses. Finally, comprehensive analyses are needed that extend beyond delivery. Current cost-effective analyses do not include the benefit of diagnosing GDM on the long-term health of the offspring despite multiple studies that report an association of GDM with early obesity and percentage of body fat. Incorporating the cost of postpartum glucose testing on women with GDM and the proposed benefit of identifying women at high risk for developing type 2 diabetes would provide a more comprehensive decision-analytic model.

The diagnostic thresholds under consideration for the diagnosis of GDM affect patients, providers, and the healthcare system. However, efforts for “real-world” implementation of the IADPSG criteria will demand efficient and cost-effective approaches to assist providers working in diverse settings to provide care to a growing number of women with GDM. Such approaches might include alternative practice models, such as group prenatal care, additional clinical staff, diabetes educators, and modified provider templates, to accommodate a greater number of high-risk women. Finally, substantial efforts will be needed by patients, providers, and the healthcare system to expand and improve adherence to postpartum glucose screening to reduce the long-term risk of type 2 diabetes in women treated for GDM.

References

1. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care.* 2011;34(Suppl 1):S11–61.

2. American Diabetes Association. Summary of revisions to the 2011 clinical practice recommendations. *Diabetes Care.* 2011;34(Suppl 1):S3.

3. Nicholson WK, Wilson LM, Witkop CT, et al. Therapeutic management, delivery, and postpartum risk assessment and screening in gestational diabetes. *Evid Rep Technol Assess (Full Rep).* 2008(162):1–96.

4. Sacks DA, Hadden DR, Maresh M, et al.; HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG Consensus Panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care.* 2012;35(3):526–528.

5. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991–2002.

6. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676–682.

7. Cundy T. Proposed new diagnostic criteria for gestational diabetes—a pause for thought? *Diabet Med.* 2012;29(2):176–180.

8. Crowther CA, Hiller JE, Moss JR, et al.; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

9. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care.* 2002;25(10):1862–1868.

10. Tovar A, Chasan-Taber L, Eggleston E, et al. Postpartum screening for diabetes among women with a history of gestational diabetes mellitus. *Prev Chronic Dis.* 2011;8(6):A124.

11. Bennett WL, Ennen CS, Carrese JA, et al. Barriers to and facilitators of postpartum follow-up care in women with recent gestational diabetes mellitus: a qualitative study. *J Womens Health (Larchmt).* 2011;20(2):239–245.

12. Meltzer SJ, Snyder J, Penrod JR, et al. Gestational diabetes mellitus screening and diagnosis: a prospective randomised controlled trial comparing costs of one-step and two-step methods. *BJOG.* 2010;117(4):407–415.

13. Nicholson WK, Fleisher LA, Fox HE, et al. Screening for gestational diabetes mellitus: a decision and cost-effectiveness analysis of four screening strategies. *Diabetes Care.* 2005;28(6):1482–1484.

14. Lavin JP Jr, Lavin B, O'Donnell N. A comparison of costs associated with screening for gestational diabetes with two-tiered and one-tiered testing protocols. *Am J Obstet Gynecol.* 2001;184(3):363–367.

15. Mission JF, Ohno MS, Cheng YW, et al. Gestational diabetes screening with the new IADPSG guidelines: a cost-effectiveness analysis. *Am J Obstet Gynecol.* June 29, 2012. [Epub ahead of print]

Evidence-based Practice Center Presentation I: Relative Hyperglycemia and Health Outcomes for the Mother and the Fetus

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There is currently no universally accepted "gold standard" for diagnosing gestational diabetes mellitus (GDM). This has resulted in the endorsement of a variety of recommended diagnostic glucose thresholds by different stakeholders. We sought to identify evidence on how, in the absence of treatment, health outcomes of mothers who meet various criteria for GDM and their offspring compare with those who do not meet the various criteria.

Thirty-eight studies provided data for this question; the majority were cohort studies or the untreated groups from randomized trials. A wide variety of diagnostic criteria and thresholds were compared across the studies. The most common groups compared were GDM diagnosed by Carpenter-Coustan criteria, no GDM by any criteria (normal), impaired glucose tolerance defined as one abnormal glucose value, and false positive (positive oral glucose challenge test, negative oral glucose tolerance test). The following criteria were used: Carpenter-Coustan (19 studies), National Diabetes Diagnostic Group (6 studies), World Health Organization (6 studies), and the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (3 studies). Tables 1 and 2 provide a summary of the maternal and fetal/neonatal outcomes, respectively, where there was more than a single study for the comparison.

A methodologically strong study showed a continuous positive relationship between increasing glucose levels and the incidence of primary cesarean section.[1]

There were 21 comparisons for cesarean section with 8 showing statistically significant differences. Patient groups with no GDM showed fewer cesarean sections when compared with Carpenter-Coustan GDM (nine studies), Carpenter-Coustan with one abnormal oral glucose tolerance test (four studies), Carpenter-Coustan false positives (five studies), and National Diabetes Diagnostic Group false positives (four studies). Four studies compared Carpenter-Coustan GDM with false positives and showed lower incidence for those with false-positive results.

For preeclampsia, significantly more cases were found for patients meeting Carpenter-Coustan criteria compared with those without GDM (three studies). For Carpenter-Coustan GDM versus false-positive groups (two studies), there were significantly fewer cases among the false positives. No differences were found for National Diabetes Diagnostic Group false positives versus no GDM (two studies) and World Health Organization impaired glucose tolerance versus no GDM (three studies).

No studies provided data on long-term maternal outcomes, such as type 2 diabetes mellitus, obesity, and hypertension.

For outcomes among the offspring, two methodologically strong studies showed a continuous positive relationship between increasing glucose levels and the incidence of macrosomia.[1,2]

Table 1. Evidence Summary Table: Maternal Outcomes

Outcome and Comparison	Studies	Participants	Risk Ratio (95% CI)	I^2 (%)	Favors* (SOE)
Cesarean Delivery					
CC false positive vs. no GDM	5	20,849	1.15 (1.07, 1.23)	0	No GDM (low)
CC one abnormal OGTT vs. no GDM	4	7,124	1.40 (1.21, 1.63)	0	No GDM (low)
CC one abnormal OGTT vs. false positive	2	529	Results not pooled due to heterogeneity	79	NSD (insufficient)
CC GDM vs. no GDM	9	51,740	1.34 (1.17, 1.48)	63	No GDM (low)
CC GDM vs. false positive	4	7,593	1.16 (1.05, 1.29)	0	False positive (low)
NDDG false positive vs. no GDM	4	4,501	1.17 (1.08, 1.28)	0	No GDM (low)
WHO IGT vs. no GDM	2	3,499	1.22 (0.90, 1.64)	42	NSD (insufficient)
Preeclampsia					
CC GDM vs. no GDM	3	17,380	1.50 (1.07, 2.11)	0	No GDM (low)
CC GDM vs. false positive	2	4,272	1.51 (1.17, 1.93)	0	False positive (low)
NDDG false positive vs. no GDM	2	3,583	1.10 (0.67, 1.83)	0	NSD (insufficient)
WHO IGT vs. no GDM	3	3,903	1.47 (0.62, 3.52)	63	NSD (insufficient)

CC = Carpenter-Coustan; GDM = gestational diabetes mellitus; IGT = impaired glucose tolerance; NDDG = National Diabetes Data Group; NSD = no significant difference; OGTT = oral glucose tolerance test; SOE = strength of evidence; WHO = World Health Organization.
*Where the result was statistically significant, we have listed the group that had the better outcome (e.g., lower incidence of preeclampsia).

Table 2. Evidence Summary Table: Fetal/Neonatal Outcomes

Outcome and Comparison	Studies	Participants	Risk Ratio (95% CI)	I^2 (%)	Favors* (SOE)
Macrosomia >4,000 grams					
IADPSG GDM vs. no GDM	2	2,130	2.09 (0.39, 11.33)	39	NSD (insufficient)
CC one abnormal OGTT vs. false positive	3	1,873	1.84 (1.12, 3.02)	3	False positive (insufficient)
CC one abnormal OGTT vs. no GDM	7	16,063	1.44 (1.13, 1.82)	14	No GDM (insufficient)
CC GDM vs. no GDM	10	42,874	1.61 (1.35, 1.92)	42	No GDM (insufficient)
CC GDM vs. false positive	5	8,241	1.36 (1.10, 1.68)	45	False positive (insufficient)
CC GDM vs. one abnormal OGTT	3	1,101	0.99 (0.92, 1.07)	0	NSD (low)
CC false positive vs. no GDM	5	14,852	1.02 (0.85, 1.24)	31	NSD (low)
NDDG false positive vs. no GDM	4	4,501	1.44 (1.10, 1.89)	0	No GDM (low)
Shoulder Dystocia					
CC GDM vs. no GDM	5	27,473	2.86 (1.81, 4.51)	0	No GDM (low)
Neonatal Hypoglycemia					
CC one abnormal OGTT vs. no GDM	4	7,124	1.29 (0.88, 1.91)	0	NSD (insufficient)
CC GDM vs. no GDM	3	7,966	Results not pooled due to heterogeneity	94	NSD (insufficient)
WHO IGT vs. no GDM	3	3,895	1.00 (0.49, 2.07)	0	NSD (insufficient)
Hyperbilirubinemia					
CC GDM vs. no GDM	2	7,854	Results not pooled due to heterogeneity	94	NSD (insufficient)
WHO IGT vs. no GDM	2	3,491	0.64 (0.38, 1.10)	0	NSD (insufficient)

CC = Carpenter-Coustan; GDM = gestational diabetes mellitus; IFG = impaired fasting glycemia; IGT = impaired glucose tolerance; IGT-2 = double impaired glucose tolerance; IADPSG = International Association of Diabetes and Pregnancy Study Groups; NDDG = National Diabetes Data Group; NSD = no significant difference; OGTT = oral glucose tolerance test; SOE = strength of evidence; WHO = World Health Organization.

*Where the result was statistically significant, we have listed the group that had the better outcome (e.g., lower incidence of macrosomia).

The most commonly reported outcome for offspring was macrosomia >4,000 grams. Fewer cases were found among patient groups with no GDM compared with Carpenter-Coustan GDM (10 studies), Carpenter-Coustan with one abnormal oral glucose tolerance test (7 studies), and National Diabetes Diagnostic Group false positives (4 studies). Significantly fewer cases were found for false positives compared with Carpenter-Coustan GDM (five studies) and Carpenter-Coustan with one abnormal oral glucose tolerance test (three studies). No significant difference was found for groups meeting criteria of the IADPSG compared with patient groups without GDM (two studies).

There were 16 comparisons for shoulder dystocia; however, few studies compared the same diagnostic thresholds or criteria. Patient groups with no GDM showed lower incidence of shoulder dystocia when compared with Carpenter-Coustan GDM (five studies).

Seven comparisons were made for neonatal hypoglycemia, and no differences were found overall. Different definitions of neonatal hypoglycemia make it difficult to draw conclusions for this outcome.

There were 15 comparisons for hyperbilirubinemia; few studies compared the same diagnostic criteria or thresholds, and a variety of definitions for hyperbilirubinemia was used.

Based on single studies, significant differences were found in the prevalence of childhood obesity for Carpenter-Coustan GDM versus groups with no GDM (lower prevalence for no GDM) and Carpenter-Coustan GDM versus false positives (lower prevalence for false positives). This study did not control for maternal weight or body mass index.[3] No other studies provided data on long-term outcomes, including type 2 diabetes mellitus and transgenerational GDM.

In summary, there was more macrosomia in neonates of women with GDM across various glucose criteria when compared with women without GDM. Preeclampsia was more common in women who met Carpenter-Coustan and IADPSG diagnostic glucose criteria for GDM compared with patient groups with no GDM. Primary cesarean delivery was more common in women who met Carpenter-Coustan or IADPSG glucose criteria compared with women without GDM. Shoulder dystocia, clinical neonatal hypoglycemia, and hyperbilirubinemia were statistically significantly less frequent in an analysis of the unadjusted Hyperglycemia and Adverse Pregnancy Outcome study data for women without an IADPSG diagnosis of GDM compared with women with a diagnosis of GDM.[4]

This question was based on information for women who did not receive treatment for GDM. These women may differ from the general population in ways that are related to the reasons for which they did not seek or receive early prenatal care (e.g., socioeconomic status). Although women with untreated GDM have a variety of poorer outcomes than women without GDM, we cannot assume that treatment of GDM reverses all the short- and long-term poor outcomes observed in women with untreated GDM. It is also unclear whether glucose intolerance is always the cause of these poorer outcomes. Many studies did not control for important potential confounders such as maternal body mass index. Some of the reasons for the poorer outcomes in women who have untreated GDM or their offspring may not be modifiable, such as the influences of genetic makeup. The strength of evidence was low or insufficient for most outcomes and comparisons in this question due to high risk of bias (observational studies), inconsistency across studies, and/or imprecise results. For many comparisons, the numbers of studies, participants, and/or events was low; therefore, findings of no statistically significant differences between groups do not imply equivalence or rule out potential differences.

References

1. Metzger B, Lowe L, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991–2002.

2. Sacks DA, Greenspoon JS, bu-Fadil S, et al. Toward universal criteria for gestational diabetes: the 75-gram glucose tolerance test in pregnancy. *Am J Obstet Gynecol.* 1995;172(2 I):607–614.

3. Hillier TA, Pedula KL, Schmidt MM, et al. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care.* 2007;30(9):2287–2292.

4. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676–682.

Relative Hyperglycemia and Health Outcomes for the Mother

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There have been multiple reports demonstrating that gestational diabetes (GDM) is a significant risk for type 2 diabetes. For example, Kim et al. reported that in women with previous GDM, the cumulative likelihood of diabetes ranged from 2.6% to more than 70% from 6 weeks through 28 years postpartum.[1] There was a rapid increase during the first 5 years after delivery for different racial groups. Fasting glucose during pregnancy was a strong and consistent predictor of postpartum diabetes. However, there is a dearth of studies examining the long-term metabolic risk associated with glucose intolerance less severe than GDM. Further complicating any analysis of metabolic outcomes in women with impaired gestational glucose tolerance are the multiple criteria used to define normal and abnormal glucose tolerance during and subsequent to pregnancy.

In a recent meta-analysis, Bellamy et al. examined the risk of type 2 diabetes after GDM.[2] Many of the reports included criteria for GDM such as the World Health Organization classification (2-hour glucose values of $\geq$140 mg/dL). This level of glucose, after an oral glucose tolerance test, is less than the 2-hour glucose value for the National Diabetes Data Group criteria of 165 mg/dL[3] or Carpenter and Coustan criteria of 155 mg/dL.[4] Therefore, these studies may well include women with glucose intolerance less than currently used for the diagnosis of GDM. Many, but not all of these studies, report an increased risk of type 2 diabetes in mothers who formerly had GDM using World Health Organization criteria for diagnosis.

Recommendations from the 5th International Workshop-Conference on Gestational Diabetes Mellitus suggest an oral glucose tolerance test 6 to 12 weeks after delivery and, if normal, repeated at 1 year and at a minimum of every 3 years thereafter.[5] Retnakaran et al. classified women as having GDM based on the National Diabetes Data Group criteria, or having one abnormal value (gestational impaired glucose tolerance), an abnormal glucose challenge test but normal oral glucose tolerance test (abnormal glucose challenge test/normal glucose tolerance) and normal glucose challenge test/normal glucose tolerance.[6] All subjects who had a normal oral glucose tolerance test at 3 months postpartum were followed prospectively. By 12 months, there was a progression to prediabetes/diabetes, from 2.8% in the normal glucose challenge test/normal glucose tolerance to 9.8% in the gestational impaired glucose tolerance group. The current recommendations for testing, even with a normal oral glucose tolerance test at 6–12 weeks, appear appropriate given the 10% increase of abnormal glucose tolerance at 1 year postpartum.

In a large retrospective cohort study, Retnakaran and Shah compared the risk of diabetes in women (n=15,381) with an abnormal 1-hour 50-gram glucose challenge test ($\geq$140 mg/dL) but normal oral glucose tolerance test with women with a normal 50-gram glucose challenge test (n=61,237).[7] In those who had a positive glucose challenge test, the rate of diabetes was 5.04 cases/1,000 person-years in comparison with 1.74 cases in those with a normal glucose challenge test. There are three long-term follow-up studies in women with one abnormal value on an oral glucose tolerance test using the Carpenter and Coustan criteria.[4] Corrado et al. showed that 6.9 years after delivery there was a significant increased risk of abnormal glucose tolerance in women with GDM (34.5%) and one abnormal value (28.7%) in comparison with normal glucose tolerance in pregnancy (9.7%).[8] Pre-pregnancy body mass index was the strongest predictive factor in both groups. In a larger retrospective cohort, Carr et al. reported

that women with one abnormal value on their oral glucose tolerance test had a twofold greater risk of diabetes compared with a normal glucose tolerance group at 8.8 years follow-up.[9] In the DIAGEST 2 study, women with one abnormal value on an oral glucose tolerance test were evaluated 6.8 years after the index pregnancy.[10] Compared with the control group with normal glucose tolerance, women with one abnormal value, as well as those with GDM, had a significant increased risk of postpartum glucose abnormalities (Table 1). The predictors of any abnormality in glucose function postpartum included ethnicity, previous GDM, pre-pregnancy body mass index greater than 27 kg/m^2, previous abnormal glucose tolerance, and socioeconomic level. In summary, there is both a short- and long-term risk of abnormal glucose testing in women with glucose intolerance less than the Carpenter and Coustan GDM criteria.[4]

Table 1. Incidence of Diabetes, Impaired Glucose Tolerance, Impaired Fasting Glucose, and "Any Abnormality" 6.8 Years After Pregnancy in Women With Previous Gestational Diabetes Mellitus, Previous One Abnormal Value, and Control Subjects[10]

	DM at Follow-up	IGT at Follow-up	IFG at Follow-up	"Any Abnormality" at Follow-up
Control	0.9% (1/111)*	2.1% (1/48)†	3.6% (4/111)*	8.3% (4/48)†
Previous OAV Comparison vs. control	6.5% (11/175)* *P*<0.05	11.3% (13/115)† *P*<0.05	6.3% (11/175)* NS	28.7% (33/115)† *P*<0.005
Previous GDM Comparison vs. control	18% (53/295)* *P*<0.001	13.4% (28/209)† *P*<0.05	8.5% (25/295)* NS	43.5% (91/209)† *P*<0.001

"Any Abnormality" = DM, IGT, and /or IFG; DM = diabetes mellitus; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OAV = one abnormal value of glucose tolerance during pregnancy.
*Number of cases/number of subjects with fasting plasma glucose measurements.
†Number of cases/number of subjects with oral glucose tolerance test measurements.

A 5-year follow-up study of GDM using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria was presented by Irish investigators at a meeting of the American Diabetes Association.[11] The prevalence of prediabetes/diabetes was 3.4% (9/265) in the normal glucose tolerance group and 26.1% (55/211) in the previous IADPSG/GDM. In a logistic regression analysis, the risk factors for development of prediabetes/diabetes included a first-degree relative with diabetes, insulin use during pregnancy, and fasting glucose $\geq$100 mg/dL. Maternal body mass index was not associated with the risk of prediabetes/diabetes. Therefore, although the primary objective of the Hyperglycemia and Adverse Pregnancy Outcome study was to assess glucose intolerance relative to adverse pregnancy outcomes, the IADPSG criteria for GDM also will function to identify women at high risk of postpartum glucose intolerance.

Because of decreased insulin sensitivity in late gestation, women with glucose intolerance during pregnancy may also have disturbances in lipid metabolism as well. Since we do not routinely measure maternal lipid concentrations during pregnancy, there may be subclinical hyperlipidemia, increasing the risk of cardiovascular disorders in later life. Retnakaran et al. characterized glucose and lipid profiles during and after pregnancy in women with varying degrees of glucose intolerance.[12] Based on an oral glucose tolerance test during pregnancy,

they characterized 482 women as previously described as having normal glucose challenge test/normal glucose tolerance, abnormal glucose challenge test/normal glucose tolerance, gestational impaired glucose tolerance at one abnormal value on an oral glucose tolerance test, and GDM. There were no significant differences in basal lipid concentrations during pregnancy, but at 3 months postpartum there were significant differences among groups. Gestational impaired glucose tolerance was an independent predictor of an atherogenic lipid profile at 3 months postpartum. Dawson, in a 20-year follow-up study, reported that pregnancy-related increases of glucose less severe than GDM were associated with an increased risk of hypertension or cardiovascular disease.[13] There was a fourfold increased risk for adverse cardiovascular outcomes across quartiles of HbA1c measured during pregnancy after adjustment for risk factors.

In conclusion, just as there is a progression to glucose intolerance postpartum in women with GDM because of failure of beta cell function to compensate for increased insulin resistance often associated with weight gain,[14] impaired glucose tolerance in pregnancy is also a clinical biomarker for women who are similarly at risk for long-term metabolic complications.

References

1. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes. *Diabetes Care.* 2002;25(10):1862–1868.

2. Bellamy L, Casas JP, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet*. 2009;373(9677):1773–1779.

3. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes.* 1979;28(12):1039–1057.

4. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol.* 1982;144(7):768–773.

5. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care*. 2007;30(Suppl 2):S251–S260.

6. Retnakaran R, Qi Y, Connelly PW, et al. Risk of early progression to prediabetes or diabetes in women with recent gestational dysglycaemia but normal glucose tolerance at 3-month postpartum. *Clin Endocrinol (Oxf)*. 2010;73(4):476–483.

7. Retnakaran R, Shah BR. Abnormal screening glucose challenge test in pregnancy and future risk of diabetes in young women. *Diabetic Med.* 2009;26(5):474–477.

8. Corrado F, D'Anna R, Cannata ML, et al. Positive association between a single abnormal glucose tolerance test value in pregnancy and subsequent abnormal glucose tolerance. *Am J Obstet Gynecol*. 2007;196(4):339.e1–339.e5.

9. Carr DB, Newton KM, Utzschneider KM, et al. Modestly elevated glucose levels during pregnancy are associated with a higher risk of future diabetes among women without gestational diabetes mellitus. *Diabetes Care*. 2008;31(5):1037–1039.

10. Vambergue A, Dognin C, Boulogne A, et al. Increasing incidence of abnormal glucose tolerance in women with prior abnormal glucose tolerance during pregnancy: DIAGEST 2 study. *Diabet Med.* 2008;25(1):58–64.

11. Noctor E, Crowe C, Avalos G, et al. Atlantic DIP: index pregnancy factors associated with progression to pre-diabetes/diabetes up to 5 years post-gestational diabetes in the west of Ireland. Poster 1324-P presented at Annual Meeting of the American Diabetes Association; June 9, 2012, Philadelphia, PA.

12. Retnakaran R, Qi Y, Connelly PW, et al. The graded relationship between glucose tolerance status in pregnancy and postpartum levels of low-density-lipoprotein cholesterol and apolipoprotein B in young women: implications for future cardiovascular risk. *J Clin Endocrinol Metab*. 2010;95(9):4345–4353.

13. Dawson SI. Glucose tolerance in pregnancy and the long-term risk of cardiovascular disease. *Diabetes Res Clin Pract*. 2009;85(1):14–19.

14. Xiang AH, Kjos SL, Takayanagi M, et al. Detailed physiological characterization of the development of type 2 diabetes in Hispanic women with prior gestational diabetes mellitus. *Diabetes.* 2010;59(10):2625–2630.

Relative Hyperglycemia and Health Outcomes for the Fetus

David J. Pettitt, M.D.

Between 1965 and 1979, prior to the formalization of screening and diagnosis of gestational diabetes mellitus (GDM), data collected during pregnancy on Pima Indian women found that, among women without known diabetes, perinatal mortality, macrosomia, preeclampsia, and cesarean section rates all varied directly with glucose concentration.[1] Almost 30 years later, the large multicenter Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study confirmed that, among women not meeting established criteria for GDM, glucose was associated with large birth weight, preeclampsia, and cesarean section.[2] In addition, this study found that rates of neonatal hypoglycemia, high C-peptide concentrations in the cord blood, premature delivery, shoulder dystocia or birth injury, hyperbilirubinemia, and admission to a neonatal intensive care unit all varied directly with maternal glucose concentration. In the HAPO study, perinatal mortality rates were low and were not statistically associated with maternal glucose, but a survey of untreated women in Brazil found that hyperglycemia below diabetes concentrations was related to perinatal mortality after 34 weeks of gestation.[3]

Recently, randomized studies designed to assess the benefit of treatment for GDM have provided data on outcomes for offspring of women with a diagnosis of GDM that was not treated. The Australian Carbohydrate Intolerance Study in Pregnant Women enrolled women who were diagnosed based on the pre-1994 World Health Organization definition of impaired glucose tolerance.[4] The World Health Organization stated that "the management of impaired glucose tolerance during pregnancy should be the same as for diabetes."[5] Therefore, women who had any fasting glucose below 140 mg/dL and a 2-hour post-75-gram-load glucose of 140 to 199 mg/dL were randomized to an intervention group, in which they were informed of the diagnosis and given a treatment plan, or to a routine care group, in which they were informed that they did not have GDM. Among infants born to the untreated women, 23 (4%) had serious complications including 5 perinatal deaths. Sixteen had shoulder dystocia, 115 (22%) were large for gestational age, and 21% weighed more than 4 kilograms.[4] Cord blood glucose concentration was significantly higher, and cord blood adiponectin and adeponectin to leptin ratios were lower than in newborns of a concurrently enrolled group of women with normal glucose tolerance.[6]

Another randomized treatment trial enrolled women with milder GDM.[7] Enrolled women met the more restrictive criteria adopted at the Fourth International Workshop-Conference on Gestational Diabetes Mellitus in 1998,[8] but those who had a fasting glucose ≥95 mg/dL, which was the diagnostic cut-point based on fasting glucose, were excluded, as were women with a 1-hour post-50-gram load screen that exceeded 200 mg/dL. This would have effectively excluded women with unrecognized preexisting diabetes. A secondary analysis of the untreated cohort along with women with lesser degrees of glucose intolerance found significant associations between glucose tolerance category and large-for-gestational-age infants, elevated cord blood C-peptide, shoulder dystocia, and preeclampsia as well as composite neonatal morbidity.[9] Data are becoming available on the outcome of pregnancies that met the criteria proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG)[10] but were not treated because at the time of the pregnancy they were considered normal. In the Atlantic Diabetes in Pregnancy study in Ireland,[11] 258 untreated women were identified as meeting the IADPSG criteria for GDM but not meeting current World Health Organization criteria.[12] The offspring had higher rates of macrosomia, large for gestational age, cesarean section, and

neonatal intensive care unit admission than offspring of women with normal glucose tolerance by the IADPSG criteria. In an Italian report,[13] 112 women with GDM by IADPSG criteria but normal by Fourth International Workshop-Conference on Gestational Diabetes Mellitus criteria[8] were identified. Their newborns had a significantly higher ponderal index and higher rates of large-for-gestational-age birth and cesarean section.

There are still few reports of what the long-term outcome will be for fetuses that were exposed to various concentrations of glucose during gestation, but HAPO investigators will soon begin examining these offspring (personal communication, BE Metzger, M.D., June 2012). Examinations were performed on 2-year-old children in the Belfast HAPO Family Study, who are the offspring of the women enrolled in the Belfast, Northern Ireland, HAPO center.[14] In that cohort, maternal glucose during pregnancy was not associated with anthropometric measurements in the children at age 2. This was not surprising given that even the offspring of women with a diagnosis of GDM have been found to be of normal weight at age 1 to 2.[15,16] However, in another study, by age 3, higher weights were found among offspring of women with a 1-hour glucose challenge test concentration ≥130 mg/dL than among offspring of women with lower glucose concentrations.[17] This higher glucose concentration would have included all women with a diagnosis of GDM by the criteria in use at the time. In a follow-up study of Pima Indian children, starting at age 5, there was a direct association between maternal 2-hour glucose concentration during a pregnancy oral glucose tolerance test and both the child's weight and 2-hour glucose concentration even if the mother did not meet the criteria for GDM.[18,19] Likewise, in a large population of women enrolled in a Kaiser Permanente Health Plan who had a normal 50-gram glucose challenge test during pregnancy, weight of children at age 5 to 7 was correlated with the 1-hour postload maternal glucose concentration.[20]

References

1. Pettit DJ, Knowler WC, Baird HD, et al. Gestational diabetes: infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in the Pima Indians. *Diabetes Care.* 1980;3(3):458–464.

2. Metzger BE, Loew LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New Engl J Med.* 2008;358(19):1991–2002.

3. Wendland EM, Duncan BB, Mengue SS, et al. Lesser than diabetes hyperglycemia in pregnancy is related to perinatal mortality: a cohort study in Brazil. *BMC Pregnancy Childbirth.* 2011;11:92. Available at: http://biomedcentral.com/1471-2393/11/92. Accessed June 26, 2012.

4. Crowther CA, Hiller JE, Moss JR, et al.; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *New Engl J Med.* 2005;352(24):2477–2486.

5. WHO Study Group. Diabetes mellitus: report of a WHO study group. World Health Organization Technical Report Series 727. Geneva, Switzerland: World Health Organization; 1985:1–113.

6. Pirc LK, Owens JA, Crowther CA, et al. Mild gestational diabetes in pregnancy and the adipoinsular axis in babies born to mothers in the ACHOIS randomized controlled trial. *BMC Pediatrics.* 2007;7:18. Available at: http://biomedcentral.com/1471-2431/7/18. Accessed June 26, 2012.

7. Landon MB, Spong CY, Thom E, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *New Engl J Med.* 2009;361(14):1339–1348.

8. Metzger BE, Coustan DR; The Organizing Committee. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care.* 1998;21(Suppl 2):B161–B167.

9. Landon MB, Mele L, Spong CY, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The relationship between maternal glycemia and perinatal outcome. *Obstet Gynecol.* 2011;117(2 Pt 1):218–224.

10. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676–682.

11. O'Sullivan EP, Avalos G, O'Reilly M, et al.; Atlantic DIP Collaborators. Atlantic Diabetes in Pregnancy (DIP): the prevalence and outcomes of gestational diabetes mellitus using new diagnostic criteria. *Diabetologia.* 2011;54(7):1670–1675.

12. WHO Study Group. Prevention of diabetes mellitus: report of a WHO Study Group. World Health Organization Technical Report Series 844. Geneva, Switzerland: World Health Organization; 1994:1–100.

13. Lapolla A, Dalfra MG, Ragazzi E, et al. New International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommendations for diagnosing gestational diabetes compared with former criteria: a retrospective study on pregnancy outcome. *Diabetic Med.* 2011;28(9):1074–1077.

14. Pettitt DJ, McKenna S, McLaughlin C, et al. Maternal glucose at 28 weeks of gestation is not associated with obesity in 2-year-old offspring: the Belfast Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Family Study. *Diabetes Care.* 2010;33(6):1219–1223.

15. Silverman BL, Rizzo T, Green OC, et al. Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes.* 1991;40:(Suppl 2):121–125.

16. Pettitt DJ. Summary and comment of Silverman BL, Rizzo T, Green OC, at al. Long-term prospective evaluation of offspring of diabetic mothers (*Diabetes* 1991;40:[Suppl 2]:121–125). *Diabetes Spectrum.* 1992;5:39–40.

17. Deierlein AL, Siega-Riz AM, Chantala K, et al. The association between maternal glucose concentration and child BMI at age 3 years. *Diabetes Care.* 2011;34(2):480–484.

18. Pettitt DJ, Bennett PH, Said MF, et al. Abnormal glucose tolerance during pregnancy in Pima Indian women: long-term effects on offspring. *Diabetes.* 1991;40(Suppl 2):126–130.

19. Franks PW, Looker HC, Kobes S, et al. Gestational glucose tolerance and risk of type 2 diabetes in young Pima Indian offspring. *Diabetes.* 2006;56(2):460–465.

20. Hillier TA, Pedula KL, Schmidt MM, et al. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care.* 2007;30(9):2287–2292.

Evidence-based Practice Center Presentation II: Benefits of Treatment of Gestational Diabetes Mellitus on Maternal and Fetal Health Outcomes

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A synthesis of the evidence commissioned by the U.S. Preventive Services Task Force and completed in 2008 found that treatment of women with mild gestational diabetes mellitus (GDM) diagnosed after 24 weeks gestation provided benefits in terms of maternal and neonatal health outcomes.[1] Specifically, a high-quality trial involving 1,000 women showed a reduction in "any serious perinatal complication" including death, shoulder dystocia, bone fracture, and nerve palsy.[2] The number of events for many of the outcomes was extremely small, which did not provide adequate evidence to make conclusions for individual outcomes. The same study showed a reduction in maternal hypertension in the treated GDM group; however, this finding may have resulted from the slight increase in gestational age at birth in the untreated GDM group.[2]

We sought to determine whether additional data were available to address the evidence gaps in the previous U.S. Preventive Services Task Force review. The question of interest was whether treatment modifies the health outcomes of mothers who meet various criteria for GDM and their offspring. The population of interest was pregnant women (≥24 weeks gestation and <24 weeks gestation) without known preexisting diabetes mellitus who meet any diagnostic threshold for GDM. Studies were included if they compared any treatment for GDM including, but not limited to, dietary advice, blood glucose monitoring, insulin therapy, and oral hypoglycemic agents with placebo or no treatment.

Eleven studies, including five randomized controlled trials (RCTs) and six retrospective cohort studies, compared diet modification, glucose monitoring, and insulin as needed with no treatment. The majority of studies were conducted in North America or Australia, in addition to two from Italy and one from Taiwan. Diagnosis (when reported) occurred at or after 24 weeks gestation. Among these studies, a variety of glucose threshold criteria were used for inclusion, varying from 50-gram screen positive with nondiagnostic oral glucose tolerance tests to women who met National Diabetes Data Group criteria for a diagnosis of GDM. The two large RCTs by Crowther et al.[2] and Landon et al.[3] used different glucose thresholds for entry in their trials: World Health Organization and Carpenter and Coustan criteria with a fasting glucose <95 mg/dL (5.3 mmol/L), respectively. The mean glucose levels at study entry were similar between these two RCTs, which may reflect a reluctance to assign women with more marked glucose intolerance to a group receiving no treatment. Table 1 provides a summary of findings.

In terms of maternal outcomes, the overall combined effect of three RCTs showed a significant difference for preeclampsia with fewer cases in the treated group (moderate strength of evidence). In two of these studies, there was no significant difference between groups in gestational age at time of delivery. One cohort study showed no significant difference in preeclampsia between groups, although the number of events was small. There was little evidence of differences in maternal weight gain based on four RCTs and two cohort studies, although the strength of evidence was considered insufficient due to inconsistency across studies and imprecision in effect estimates. No differences between groups were found for rates of cesarean section (five RCTs, six cohorts) or unplanned cesarean section (one RCT, one

Table 1. Strength of Evidence for Studies Comparing Treatment With No Treatment of Women With Gestational Diabetes Mellitus

Outcome			
Preeclampsia	Three RCTs (2,014)	Moderate (favors treatment)	The evidence provides moderate confidence that the estimate reflects the true effect of less preeclampsia in the treatment group.
	One cohort (258)	Insufficient	
Maternal weight gain	Four RCTs (2,530)	Insufficient	There is insufficient evidence to draw conclusions for this outcome due to inconsistency across studies and imprecise effect estimates.
	Two cohorts (515)	Insufficient	
Cesarean section	Five RCTs (2,613)	Low (no difference)	The evidence provides low confidence that the estimate reflects the true effect. The results are inconsistent across study designs.
	Six cohorts (3,110)	Insufficient	
Birth injury	Two RCTs (1,230)	Low	There is insufficient evidence to make a conclusion for this outcome. There is a difference in findings for the RCTs and cohort studies; the number of events and participants across all studies does not allow for a conclusion.
	One cohort (389)	Insufficient	
Shoulder dystocia	Three RCTs (2,044)	Moderate (favors treatment)	The evidence provides moderate confidence that the estimate reflects the true effect of less shoulder dystocia in the treatment group.
	Four cohorts (3,054)	Low (favors treatment)	

RCT = randomized controlled trial.

Table 1. Strength of Evidence for Studies Comparing Treatment With No Treatment of Women With Gestational Diabetes Mellitus *(continued)*

Outcome	No. of Studies (No. Patients)	Overall Strength of Evidence	Comment
Neonatal hypoglycemia	Four RCTs (2,367)	Low (no difference)	The evidence provides low confidence that there is no difference between groups.
	Two cohorts (2,054)	Insufficient	
Macrosomia (>4,000 grams)	Five RCTs (2,643)	Moderate (favors treatment)	The evidence provides moderate confidence that the estimate reflects the true effect of less macrosomia in the treatment group.
	Six cohorts (3,426)	Insufficient	
Long-term metabolic outcomes: impaired glucose tolerance	One RCT (89)	Insufficient	There is insufficient evidence to draw conclusions for this outcome.
Long-term metabolic outcomes: type 2 diabetes mellitus	One RCT (89)	Insufficient	There is insufficient evidence to draw conclusions for this outcome.
Long-term offspring metabolic outcomes: body mass index (assessed as >85th and >95th percentile)	Two RCTs (284)	Low (no difference)	The evidence provides low confidence that there is no difference between groups.

RCT = randomized controlled trial.

cohort). There was inconsistency across studies for induction of labor with no difference found for the two RCTs overall and significantly fewer inductions reported in the treatment group for one cohort study. The result observed in the cohort study may have been due to confounding by indication, because the study protocol specified delivering untreated women, who all presented with GDM at greater than 37 weeks gestation, within 1 week of GDM diagnosis. There were no data from included studies of an effect of treatment for GDM on long-term maternal outcomes such as type 2 diabetes mellitus, obesity, and hypertension.

In terms of outcomes among the offspring, there was insufficient evidence to draw conclusions for birth trauma. Two RCTs showed no difference between groups, whereas one cohort study showed less birth trauma in the treated group. The low number of events and participants across all studies resulted in imprecise estimates. The pooled result for shoulder dystocia showed a significantly lower incidence in the treated group (three RCTs, four cohorts). Overall, the evidence for shoulder dystocia was considered moderate showing less shoulder dystocia in the treated group. There was low evidence of no difference between groups for neonatal hypoglycemia based on four RCTs and two cohort studies. For macrosomia >4,000 grams, results were inconsistent across study designs: pooled results from five RCTs showed fewer cases in the treated group, and pooled results from six cohort studies showed no difference between groups, although results for the cohort studies showed substantial heterogeneity. Based on the RCTs, we assessed the strength of evidence to be moderate for macrosomia >4,000 grams, suggesting a benefit of treatment. There was no difference in hyperbilirubinemia for the three RCTs, whereas one cohort study showed less hyperbilirubinemia in the treated group. There were no differences observed across studies for perinatal death (three RCTs, three cohorts).

Few studies provided data on long-term outcomes in offspring. One RCT followed patients for 7 to 11 years and found no differences for impaired glucose tolerance or type 2 diabetes mellitus; the strength of evidence was considered insufficient due to the small sample size and small number of events. No differences were observed in single studies that assessed body mass index >95 percentile (7- to 11-year follow-up) and body mass index >85 percentile (4- to 5-year follow-up). Overall, pooled results showed no difference in body mass index and the strength of evidence was considered low.

In summary, there were significantly fewer cases of preeclampsia and shoulder dystocia among women (and offspring) who were treated for GDM compared with those not receiving treatment. There also was evidence from RCTs showing significantly fewer cases of macrosomia (>4,000 grams) among offspring of women who received treatment for GDM. There was little evidence showing differences in other key maternal and infant outcomes between groups. There was limited evidence for some outcomes, particularly the long-term outcomes. Moreover, for some outcomes, events were rare and the studies may not have had the power to detect clinically important differences between groups; therefore, findings of no significant difference should not be interpreted as equivalence between groups. For outcomes where results were inconsistent between studies, different study glucose threshold entry criteria did not explain the variation. One might have expected different treatment responses based on the magnitude of glucose intolerance of the women studied, but this pattern was not apparent between studies with different glucose inclusion criteria.

References

1. Hillier TA, Vesco KK, Pedula KL, et al. Screening for gestational diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2008;148(10):766–775.

2. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

3. Landon MB, Spong CY, Thom E, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339–1348.

Benefits of Treatment of Gestational Diabetes Mellitus on Maternal Health Outcomes

Mark B. Landon, M.D.

Gestational diabetes mellitus (GDM) represents a heterogeneous group of women with a wide spectrum of metabolic abnormalities and varying degrees of pregnancy-associated risk. With controversy surrounding appropriate diagnostic criteria for GDM as well as the value of treatment, attention has been paid primarily to perinatal outcomes such as macrosomia in the evaluation of recent large-scale observational studies and randomized trials. A recent systematic review and meta-analysis concluded that treatment of GDM is associated with a reduction in both the incidence of shoulder dystocia and macrosomia.[1] Among maternal outcomes, this report failed to show a reduction in cesarean delivery with treatment but did not consider preeclampsia/pregnancy-induced hypertension in the summary conclusions. This presentation will address two important maternal outcomes: *preeclampsia/pregnancy-induced hypertension* and *cesarean delivery* in relation to GDM. The frequency of these complications will be discussed along with the existing evidence regarding the benefit of treatment for these specific outcomes.

Preeclampsia/Gestational Hypertension

There is general agreement that preeclampsia and gestational hypertension are more common in pregnancy complicated by preexisting diabetes compared with the normal population.[2] Most authors have concluded such is the same for GDM, with frequencies varying between 5% and 22% for GDM pregnancies compared with 4.9% to 10.5% for controls (Table 1). Importantly, not all studies have carefully adjusted for confounding variables such as obesity. Two studies that matched controls to women with GDM for age, parity, and body mass index did reveal significantly higher rates of preeclampsia/gestational hypertension in GDM.[3,4] Recently, Catalano and colleagues reported a secondary analysis of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study and found that both maternal obesity and GDM were independently associated with preeclampsia.[5] GDM without obesity was associated with a 5.9% frequency of preeclampsia compared with 3.5% in lean controls. Obese women without GDM were found to have a 13.3% frequency compared with 20.1% if both GDM and obesity were present.

A large retrospective study of 1,813 GDM pregnancies included 174 cases (9.6%) of preeclampsia, a figure significantly higher than the 7.4% in the nondiabetic population.[6] In this analysis, the rate of preeclampsia increased progressively with fasting glucose level on the diagnostic oral glucose tolerance test such that a fasting value less than 95 mg/dL was associated with a 7% rate compared with 20% when the fasting level exceeded 125 mg/dL. In a logistic regression model, only pre-pregnancy body mass index (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.16–2.30) and severity of GDM (OR 1.7, 95% CI 1.21–2.38) were independently and significantly associated with the risk of preeclampsia. Glycemic control during gestation also appeared to affect the risk of developing preeclampsia. In women who achieved the targeted level of glycemic control (well controlled designated as a mean glucose less than or equal to 95 mg/dL throughout pregnancy), no difference in the rate of preeclampsia was found, even in the subgroup of women with marked elevation of fasting glucose on the diagnostic oral glucose tolerance test. In contrast, in less optimally controlled women, a significant increase in the rate of preeclampsia was observed.[6]

Table 1. Frequency of Preeclampsia/Gestational Hypertension in Treated Gestational Diabetes Mellitus

GDM (%)	Controls (%)	*P*	Authors (Ref)
141/2,461 (5.8)	374/4,922 (7.6)	NS	Langer[7]
10/197 (5.0)	12/197 (6.2)	NS	Schaffir[8]
146/874 (17.0)	7532/61,209 (12.0)	<0.001	Casey[9]
28/143 (19.6)	15/143	<0.05	Jensen[3]
16/57 (21.9)	1632/21,377 (7.1)	<0.05	Roach[4]
174/1,813 (9.6)	—— (7.4)	——	Yogev[6]
149/2,518 (5.9) (Lean)	570/16,238 (3.5) (Lean)	OR=1.74	Catalano[5]
147/730 (20.1) (Obese)	250/1,878 (13.3) (Obese)	OR=3.91	Catalano[5]

GDM = gestational diabetes mellitus; NS = not significant; OR = odds ratio.

An apparent relationship also exists between maternal glucose levels lower than those diagnostic of GDM and the rate of preeclampsia. Joffe found that 1-hour post-50-gram-challenge levels were correlated with the risk for preeclampsia in nondiabetic individuals.[10] In the HAPO study, the significant continuous association between maternal glycemia and various adverse pregnancy outcomes was confirmed. This analysis of more than 25,000 pregnancies demonstrated strong associations between glycemia and preeclampsia across the spectrum of glucose values, for which the OR for each one standard deviation in each glucose measure on the 75-gram oral glucose tolerance test ranged from 1.21 to 1.28.[11] A secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network GDM randomized treatment trial also revealed a monotonic relationship between maternal glycemia and preeclampsia/gestational hypertension.[12] A significant trend was present for all postglucose load levels (1, 2, and 3 hours) and hypertensive disorders of pregnancy. However, logistic regression analysis controlling for maternal body mass index, parity, and race did not demonstrate any elevated risk for fasting levels less than 95 mg/dL. In this analysis, women with one abnormal value on the 3-hour diagnostic oral glucose tolerance test had a rate of preeclampsia/gestational hypertension similar to untreated women with mild GDM (13%).

Recognizing that an association exists between maternal glycemia and risk for hypertensive disorders of pregnancy leads to the question as to whether treatment of GDM reduces this specific risk. Glucose levels that exceed established clinical targets (suboptimal control) as noted do appear to increase the risk for preeclampsia in women treated for GDM.[6] However, what is the evidence that treatment confers a benefit in women with minimal or mild carbohydrate intolerance during pregnancy? Remarkably, both large-scale randomized controlled trials (RCTs) for the treatment of mild GDM demonstrated a reduction in maternal hypertensive disorders with standard treatment (nutrition intervention and insulin as necessary).

In the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), treatment was associated with a 12% rate of preeclampsia compared with 18% in the control population (adjusted OR=0.70, 95% CI 0.51–0.95).[13] The NICHD MFMU trial included a group of women with milder GDM than the ACHOIS study (93% treated with dietary intervention alone), yet the combined rate of preeclampsia/gestational hypertension was reduced from 13.6% to 8.6% (p=0.01).[14]

Evidence that the treatment effect of lowering the rates of hypertensive disorders of pregnancy demonstrated in the two RCTs can be extended to populations with glucose levels lower than those meeting the entry criteria for these trials is lacking. More than 20 years ago, Langer and colleagues first randomly assigned women with one abnormal oral glucose tolerance test value to treatment versus no treatment.[15] Similar rates of hypertensive disorders were observed in treated women compared with controls. In a later prospective population-based study of more than 2,400 GDM women including one-third of subjects with one abnormal oral glucose tolerance test value, Langer and colleagues reported that intensified management failed to lower preeclampsia rates (5.9%) compared with conventional treatment of GDM.[7] Moreover, rates were not reduced compared with a control non-GDM population. A recent secondary analysis of the HAPO population was performed to determine whether associations exist between fasting C-peptide, body mass index, and maternal glucose and the risk for preeclampsia.[16] Strong independent associations were present for both C-peptide and body mass index; however, weaker relationships were found for maternal glucose especially after adjustment for confounders. In one model, no association was found for fasting glucose and preeclampsia. Together, these results do not suggest a high likelihood that treatment at lower levels of glucose than currently employed diagnostic thresholds would substantially reduce the frequency of hypertensive disorders of pregnancy.

Cesarean Delivery

The incidence of cesarean delivery is increased in GDM women compared with the normal obstetric population. Reports from over a decade ago cite cesarean rates in excess of 30% in GDM compared with approximately 20% in nondiabetic women (Table 2). The outcome of cesarean delivery is subject to many confounders, which include both maternal demographics as well as physician practice style or preferences. These factors can contribute to substantial variation in cesarean rates. Issues unique to diabetic pregnancy that appear to increase cesarean rates include maternal obesity, excessive fetal size, and physician concern about the potential for traumatic birth injury, particularly when a large fetus is suspected. This latter concern was highlighted by Naylor and colleagues, who reported that although infant macrosomia was reduced and birth weights were normalized with treatment of GDM, a clear increased risk for cesarean delivery was present in their population of women treated for GDM whether macrosomia was present or not.[17] They found that the increased risk for cesarean delivery among women treated for GDM compared with normal controls persisted after controlling for multiple maternal risk factors (adjusted OR=2.1, 95% CI 1.3–3.6). Others have similarly reported cesarean delivery rates that are higher in treated GDM women compared with the general population, even when treatment lowered macrosomia rates.[18] Thus, recognition of GDM may lead to a lower threshold for surgical delivery, which could mitigate in part the benefits of treatment.

Table 2. Frequency of Cesarean Delivery in Treated Gestational Diabetes Mellitus

GDM (%)	Controls (%)	*P*	Authors (Ref)
48/143 (33.6)	585/2,940 (20.2)	<0.001	Naylor[17]
260/874 (30.0)	10,223/61,209 (17.0)	<0.001	Casey[9]
47/143 (32.9)	30/143 (21.0)	<0.05	Jensen[3]
172/1,145 (15.0)*	674/4,922 (13.7)	NS	Langer[7]
564/2,442 (23.1)† (Lean)	2,522/15,673 (16.1)† (Lean)	OR=1.25	Catalano[5]
215/749 (28.7)† (Obese)	430/1,868 (23.0)† (Obese)	OR=1.71	Catalano[5]

GDM = gestational diabetes mellitus; NS = not significant; OR = odds ratio.
*Intensified treated GDM.
†Includes primary cesareans only.

Obesity is a clear risk for cesarean delivery and must be considered in analyses concerning mode of delivery in GDM. In Catalano's secondary analysis of the HAPO study, both GDM (using International Association of Diabetes and Pregnancy Study Groups criteria for diagnosis) and obesity independently increased the risk for primary cesarean (23% in both groups—obese non-GDM and GDM without obesity) compared with controls (16.1%).[5] The combination of obesity and GDM had even greater impact, because the primary cesarean rate rose to 28.7% in this group.

Langer et al., in a now 20-year-old large-scale prospective observational study of 2,460 GDM women, reported that intensive treatment of GDM lowered the overall cesarean rate to 15.0%, a rate not significantly different than the 13.7% of the general population.[7] In contrast, conventional treatment was associated with a marked increased rate of 21.5%. In the absence of RCTs for GDM, Langer and colleagues in 2005 addressed the consequences of not treating GDM in a matched control study of 555 gravidas who were not treated until 37 weeks and 1,110 treated subjects who were analyzed in addition to 1,110 controls.[18] Much like Naylor's earlier study, these authors found that although treatment significantly lowered macrosomia rates compared with late or no treatment, cesarean rates were not affected by treatment and remained higher than the normal population (23% vs. 14%).

Crowther and colleagues in the ACHOIS RCT reported that overall cesarean rates were not lowered with treatment of GDM (31% vs. 32%) compared with untreated controls.[13] In contrast, the NICHD MFMU trial suggested that treatment of mild GDM lowered cesarean delivery rates.[14] Cesarean delivery occurred in 26.9% of treated subjects versus 33.8% in controls (p=0.02). After excluding cases of abnormal presentation, previa, oligohydramnios, and prior cesarean delivery, the cesarean delivery rate remained lower in the treatment group than in the control group (13.0% vs. 19.7%) (p=0.01). The extent to which a reduction in large-for-gestational-age infants contributed to the lowering of the cesarean rate is unknown.

The evidence that a treatment effect for lowering of cesarean rates in women with lower glucose levels than those meeting Carpenter and Coustan criteria or other longstanding thresholds for diagnosis is limited. In Langer's RCT of treatment of women with one abnormal oral glucose tolerance test value, treatment was associated with a primary cesarean rate of 10% compared with 11% in controls (not significant).[15] In the HAPO study, the OR for cesarean delivery increased among glucose categories and was 1.86 with the highest 1-hour glucose.[11] However, cesarean was only modestly increased relative to fetal macrosomia. Moreover, the OR was not significantly increased in the highest 2-hour category. In the fasting category, primary cesarean rates ranged from 13.3% to 27% in the highest category. Differences in rates (21%–24%) were not remarkably different in categories 4 through 6, corresponding to fasting levels of 85–89 mg/dL, 90–94 mg/dL, and 95–99 mg/dL, respectively. Given these relationships and the relative lack of convincing treatment effect on cesarean section rates except for the NICHD MFMU RCT, it follows that lowering of diagnostic thresholds and treatment as such would be unlikely to further reduce cesarean delivery rates among GDM women.

References

1. Horvath K, Koch K, Jeitler K, et al. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. *BMJ.* 2010;340:c1395.

2. Sibai BM, Caritis S, Hauth J, et al. Risks of preeclampsia and adverse neonatal outcomes among women with pregestational diabetes mellitus. *Am J Obstet Gynecol.* 2000;182(2):364–369.

3. Jensen DM, Sorensen B, Feilberg-Jørgensen N, et al. Maternal and perinatal outcomes in 143 Danish women with gestational diabetes and 143 controlled with similar risk profile. *Diabet Med.* 2000;17(4):281–286.

4. Roach VJ, Hin LY, Tam WH, et al. The incidence of pregnancy-induced hypertension among patients with carbohydrate intolerance. *Hypertens Pregnancy.* 2000;19(2):183–189.

5. Catalano PM, McIntire HD, Cruickshank JK, et al.; HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care.* 2012;35(4):780–786.

6. Yogev Y, Xenakis EM, Langer O. The association between preeclampsia and the severity of gestational diabetes: the impact of glycemic control. *Am J Obstet Gynecol.* 2004;191(5):1655–1660.

7. Langer O, Rodriguez DA, Xenakis EM, et al. Intensified versus conventional management of gestational diabetes. *Am J Obstet Gynecol.* 1994;170(4):1036–1047.

8. Schaffir JA, Lockwood CJ, Lapinski R, et al. Incidence of pregnancy-induced hypertension among gestational diabetics. *Am J Perinatal.* 1995;12(4):252–254.

9. Casey BM, Lucas MJ, Mcintire DD, et al. Pregnancy outcomes in women with gestational diabetes compared with the general obstetric population. *Obstet Gynecol.* 1997;90(6):869–873.

10. Joffe GM, Esterlitz JR, Levine RJ, et al. The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. *Am J Obstet Gynecol.* 1998;179(4):1032–1037.

11. Metzger BE, Lowe LP, Dyer AR; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991–2002.

12. Landon MB, Mele L, Spong CY, et al. The relationship between maternal glycemia and perinatal outcome. *Obstet Gynecol.* 2011;117(2 Pt 1):218–224.

13. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

14. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339–1348.

15. Langer O, Anyaegbunam A, Brustman L, et al. Management of women with one abnormal oral glucose tolerance test value reduces adverse outcome in pregnancy. *Am J Obstet Gynecol.* 1989;161(3):593–599.

16. Yogev Y, Chen Y, Hod M, et al.; Hyperglycemia and Adverse Pregnancy Outcome Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: preeclampsia. *Am J Obstet Gynecol.* 2010;202(3):255.e1–7.

17. Naylor CD, Sermer M, Chen E, et al.; Toronto Trihospital Gestational Diabetes Investigators. Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? *JAMA.* 1996;275(15):1165–1170.

18. Langer O, Yogev Y, Most O, et al. Gestational diabetes: the consequences of not treating. *Am J Obstet Gynecol.* 2005;192(4):989–997.

Benefits of Treatment of Gestational Diabetes Mellitus on Fetal/Infant Health Outcomes

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Among the several criteria for a worthwhile screening program, one is that interventions to improve the screened-for condition are effective in improving health outcomes. Moreover, the interventions must be more useful at the time of screening than they are at a later time point in the development of the conditions. In the case of gestational diabetes mellitus (GDM), health outcomes accrue to both mother and offspring, some in the short term and some in the long term. This presentation is about the effectiveness of GDM treatment (and prevention) in lowering the risk of adverse short- and long-term outcomes in the offspring.

The short-term consequences of GDM for the offspring are well known. These include birth defects, which are related to early pregnancy hyperglycemia, and a number of perinatal complications consequent to insulin resistance and hyperglycemia in later pregnancy, which result in excess maternal fuels (e.g., glucose) crossing the placenta and fetal hyperinsulinemia. These complications include macrosomia, which can cause birth injury or lead to cesarean section, increased risk for respiratory distress syndrome, and neonatal metabolic conditions such as hypoglycemia, hypocalcemia, and hyperbilirubinemia.[1] The Hyperglycemia and Adverse Pregnancy Outcome study and observational analyses of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network and Australasian Collaborative Trial of Supplements With Vitamin C and Vitamin E for the Prevention of Preeclampsia have shown that these complications are related in a graded fashion to maternal level of fasting or postchallenge glucose during pregnancy.[2–4] It is important to note, however, that the observation of a graded relationship does not mean that interventions to treat mild forms of insulin resistance or hyperglycemia are effective in reducing these complications, or that screening for such mild abnormalities amounts to a useful approach. In addition to intervention effectiveness, criteria for a useful screening program include evidence of precision, validity, prediction, effectiveness, lack of harm, and cost-effectiveness in real-world practice settings.

In recent years, there is more attention on long-term adverse sequelae of GDM. With the rise of diabetes in general, and GDM in particular, across the world, there is increasing unease about the prospect of diabetes propagating across generations. Animal experiments going back as far as the 1970s have shown that experimentally induced GDM can result in offspring adiposity.[5] If the offspring is female, then she is more likely to develop GDM when she becomes pregnant, leading to an intergenerational cycle of diabetes and obesity. Whether this phenomenon occurs in humans has been harder to prove, in part because of the large sample sizes required, the need to separate GDM from preexisting type 1 and type 2 diabetes, and the challenges of overcoming confounding, especially by maternal body size, which is the strongest risk factor for GDM and also related to offspring obesity and metabolic risk via pathways unrelated to GDM. Although babies born to mothers with GDM are larger in weight and fat mass at birth, they lose excess weight in the first months of infancy,[6] and the extent to which any GDM-associated excess adiposity reappears later in childhood is not clear. In a recent systematic review of 12 observational studies of GDM and the risk of offspring obesity, Kim et al. found that only 2 of them compared GDM with no diabetes and adjusted for maternal body mass index; 1 reported a slightly increased risk, the other slightly decreased, and both had relatively wide confidence intervals.[7] In the first of these two studies, among approximately 14,000 children age 9–14,

Gillman et al. reported that GDM was associated with an adjusted odds ratio (OR) of 1.2 (95% confidence interval [CI] 0.8–1.7) for obesity.[8] In the other, among approximately 10,000 9- to 11-year-old children, Lawlor et al. reported an OR of 0.6 (95% CI 0.3–1.2).[9] Thus, although GDM is clearly associated with increased size and fat mass at birth, the extent to which it predicts obesity and its sequelae in the growing child is still under investigation.

Although observational studies have many advantages, including the ability to examine timing, duration, and severity of GDM, they all suffer from the potential for confounding. Only relatively large randomized controlled trials (RCTs) can overcome this limitation with sureness. Two high-quality RCTs have addressed the effects of treating mild to moderate GDM on newborn outcomes. In the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), Crowther et al. randomly assigned 1,000 women at 24 to 34 weeks gestation, whose plasma glucose level was less than 7.8 mmol/L (140 mg/dL) after an overnight fast and was 7.8 to 11.0 mmol/L at 2 hours after a 75-gram load, to usual care or to an intervention consisting of dietary advice, glucose monitoring, and insulin if necessary.[10] In the NICHD MFMU Network trial,[11] eligible women had a fasting glucose less than 5.3 mmol/L (95 mg/dL) and at least two of three levels exceeding the following cut-points after a 100-gram load: at 1 hour 10.0 mmol/L, at 2 hours 8.6 mmol/L, and at 3 hours 7.8 mmol/L. Like ACHOIS, the intervention group received nutritional counseling and insulin if necessary, and the control group received usual care.

The results of the two RCTs were roughly equivalent. Both reduced macrosomia by about one-half. The MFMU trial also measured neonatal fat mass by anthropometry; the intervention reduced it from 464 grams to 427 grams. Shoulder dystocia was reduced in the MFMU trial; this was not demonstrably so in ACHOIS, but shoulder dystocia was part of a composite outcome that the ACHOIS intervention reduced. Cesarean delivery was reduced in the MFMU trial, but unchanged in ACHOIS. Inductions and admissions to a neonatal intensive care unit were increased in ACHOIS but unaffected in the MFMU trial. In sum, both trials showed that treatment of mild to moderate GDM had favorable effects on newborn outcomes. In a subsequent analysis of ACHOIS, Moss et al. estimated that the incremental cost-effectiveness of preventing one serious perinatal complication was approximately $27,500.[12] They also estimated that the cost per discounted life-year gained was about $3,000, but this estimate is subject to many uncertainties.

Assessing outcomes in older children whose mothers participated in RCTs of treatment for GDM can provide a relatively unbiased assessment of the long-term effects of GDM, with the caveats that RCTs have strict eligibility criteria that limit generalizing findings to milder or more severe GDM, and the effects apply only to treatment, not prevention, of GDM. In a study that linked trial data from offspring of a subset of women participating in ACHOIS with height/weight surveillance data from South Australia, Gillman et al. found no effects of GDM treatment on body mass index or overweight status at age 4–5.[13]

In sum, RCTs of treatment of mild to moderate GDM are in broad agreement with the observational data. GDM is a predictor of several newborn complications, and treatment can reduce their risk. On the other hand, the literature is mixed with regard to the extent to which GDM predicts long-term offspring obesity-related outcomes, and one study of treatment did not show an effect on reducing child body mass index.

Treatment of milder GDM is a key issue in the decision of whether to lower the glucose cut-points for intervention after screening during midpregnancy. In a recent Cochrane review, Han et al. included four RCTs with a total of 521 women with borderline GDM and their babies.[14] Although these trials suggested a reduction in macrosomia (risk ratio 0.38 [95% CI 0.19 to

0.74])—but no change in cesarean section rates—the authors were circumspect because of moderate to high risk of bias in three of the four studies; the one study with low risk of bias had only 12 participants. The small overall number of participants in these four studies limited the ability to examine important but uncommon outcomes. At least two trials are ongoing.

An attractive alternative to treatment of GDM is prevention, because it does not require screening, follow-up testing, and intensive treatment, all of which are resource intensive. In addition, prevention may be especially useful for reducing the complications of milder forms of GDM because screen-and-treat strategies for less severe forms of disease are typically less cost effective. A major impediment to widespread prevention strategies is that pre-pregnancy body mass index is by far the strongest predictor of GDM, which implies that the impossible task of solving the entire obesity epidemic among young women is necessary to prevent GDM. Nevertheless, some trials during pregnancy have shown promise. In a systematic review and meta-analysis of 19 controlled trials, Oostdam et al. reviewed six types of interventions, including medication (metformin), probiotics, provision of specific diets (e.g., low glycemic index), dietary counseling, weight self-monitoring, and exercise training.[15] Some of them appeared to lower the risk of GDM, whereas others lower the prevalence of macrosomia. However, sample sizes were small and quality of most studies was low, including the fact that in some trials investigators assigned participants to treatment arms other than by random allocation.

One other type of intervention, bariatric surgery, is not a candidate for widespread use but has the potential to be effective for very obese patients and may provide proof of physiological principles. In a 2008 review, Maggard et al. concluded that rates of GDM may be lower among obese women who become pregnant after bariatric surgery versus not having had bariatric surgery.[16] A recent chart review study of 70 women undergoing bariatric surgery before pregnancy, each with four body mass index-matched comparison participants, suggested a 90% relative reduction in the incidence of GDM but a threefold increase in the prevalence of small for gestational age at birth.[17] Other studies have identified additional risks associated with obesity surgery in pregnant women, including anemia, endocrine disorders, chronic hypertension, and increased rates of cesarean section.[18] In the absence of RCTs, the best data come from studies of consecutive pregnancies in the same mother, but the number of subjects in such studies to date is small. In sum, the data on benefits and risks of bariatric surgery—including type of surgery—for pregnancy outcomes are still scarce enough to warrant caution in recommending such procedures for prevention of GDM.

Ultimately, in the decision about whether to change screening approaches, the effectiveness of intervention is only one piece. To be useful, a screening program must meet several additional criteria. Some are about the testing, including reproducibility and validity (i.e., prediction of outcomes); others are about the effectiveness of early versus later interventions; still others are about the cost-effectiveness of the entire program. An overarching principle is that screening should be held to a higher standard than diagnosis, because clinicians perform screening on asymptomatic patients. The best evidence for a screening program comes from an RCT of screening itself, that is, comparing different screen-and-treat strategies with one another. In the case of GDM, such a study could compare old and new definitions of GDM based on different glucose loads and number of failed cut-points for diagnosis and treatment.

References

1. Hay WW Jr. Care of the infant of the diabetic mother. *Curr Diab Rep.* 2012;12(1):4–15.

2. Ju H, Rumbold AR, Willson KJ, et al. Borderline gestational diabetes mellitus and pregnancy outcomes. *BMC Pregnancy Childbirth.* 2008;8:31.

3. Landon MB, Gabbe SG. Gestational diabetes mellitus. *Obstet Gynecol.* 2011;118(6):1379–1393.

4. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991–2002.

5. Aerts L, Van Assche FA. Animal evidence for the transgenerational development of diabetes mellitus. *Int J Biochem Cell Biol.* 2006(5–6);38:894–903.

6. Parker M, Rifas-Shiman SL, Belfort MB, et al. Gestational glucose tolerance and cord blood leptin levels predict slower weight gain in early infancy. *J Pediatr.* 2011;158(2):227–233.

7. Kim SY, England JL, Sharma JA, et al. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: a systematic review. *Exp Diabetes Res.* 2011;2011:541308.

8. Gillman MW, Rifas-Shiman S, Berkey CS, et al. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics.* 2003;111(3):e221–226.

9. Lawlor DA, Fraser A, Lindsay RS, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. *Diabetologia.* 2010;53(1):89–97.

10. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

11. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339–1348.

12. Moss JR, Crowther CA, Hiller JE, et al. Costs and consequences of treatment for mild gestational diabetes mellitus—evaluation from the ACHOIS randomised trial. *BMC Pregnancy Childbirth.* 2007;7:27.

13. Gillman MW, Oakey H, Baghurst PA, et al. Effect of treatment of gestational diabetes mellitus on obesity in the next generation. *Diabetes Care.* 2010;33(5):964–968.

14. Han S, Crowther CA, Middleton P. Interventions for pregnant women with hyperglycaemia not meeting gestational diabetes and type 2 diabetes diagnostic criteria. *Cochrane Database Syst Rev.* 2012;1:CD009037.

15. Oostdam N, van Poppel MN, Wouters MG, et al. Interventions for preventing gestational diabetes mellitus: a systematic review and meta-analysis. *J Womens Health (Larchmt).* 2011;20(10):1551–1563.

16. Maggard MA, Yermilov I, Li Z, et al. Pregnancy and fertility following bariatric surgery: a systematic review. *JAMA.* 2008;300(19):2286–2296.

17. Lesko J, Peaceman A. Pregnancy outcomes in women after bariatric surgery compared with obese and morbidly obese controls. *Obstet Gynecol.* 2012;119(3):547–554.

18. Belogolovkin V, Salihu HM, Weldeselasse H, et al. Impact of prior bariatric surgery on maternal and fetal outcomes among obese and non-obese mothers. *Arch Gynecol Obstet.* 2012;285(5):1211–1218.

Evidence-based Practice Center Presentation III: Harms of Treatment of Gestational Diabetes Mellitus and Relationship to Diagnostic Threshold

Lois E. Donovan, M.D., FRCPC, and Lisa Hartling, Ph.D.

A synthesis of the evidence commissioned by the U.S. Preventive Services Task Force and completed in 2008 found no evidence of harms associated with treating gestational diabetes mellitus (GDM), although the available evidence was sparse and the review authors observed that these events may be rare and may not be observed in trials.[1] Potential harms of treatment may include small-for-gestational-age neonates, maternal stress, and additional costs, including those associated with laboratory testing as well as patient and clinician time.[2] Clinician time can include the physician as well as diabetes educators, nutritionists, and other providers of obstetrical care. Healthcare provider apprehension over the diagnosis of GDM is a potential harm that could result in additional, and possibly unnecessary or overly aggressive, fetal and neonatal surveillance and delivery management. Evidence from a large randomized controlled trial (RCT) suggests that the label of GDM, regardless of need, appears to influence the care provided as evidenced by higher neonatal intensive care unit admission rates for the babies of women treated for GDM.[3]

We sought to determine whether additional data were available to address the evidence gaps in the previous U.S. Preventive Services Task Force review. The question of interest asked about the harms of treating GDM and whether they vary by diagnostic approach. The population of interest was pregnant women (≥24 weeks gestation and <24 weeks gestation) without known preexisting diabetes mellitus who meet any diagnostic threshold for GDM. Studies were included if they compared any treatment for GDM including dietary advice, blood glucose monitoring, insulin therapy, and oral hypoglycemic agents with placebo or no treatment. Outcomes of interest included anxiety, healthcare system issues, burden on practitioner's office, increased interventions due to treatment bias (e.g., increased cesarean sections or inductions of labor), postpartum depression, small-for-gestational-age neonates, costs, and resource allocations.

Five studies (four RCTs, one cohort study) compared diet modification, glucose monitoring, and insulin as needed with no treatment. Three studies were conducted in the United States and one each in Italy and Australia. Timing of diagnosis of GDM occurred at or after 24 weeks gestation. Among these studies, a variety of glucose threshold criteria were used for inclusion, varying from 50-gram screen positive with nondiagnostic oral glucose tolerance tests to World Health Organization criteria for a diagnosis of GDM. The two largest RCTs by Crowther et al.[3] and Landon et al.[4] used different glucose thresholds for entry in their trials: World Health Organization and Coustan and Carpenter criteria with a fasting glucose <95 mg/dL (5.3 mmol/L), respectively. The mean fasting glucose levels at study entry were similar between these two trials, which may reflect a reluctance to assign women with more marked glucose intolerance to a group receiving no treatment.

There were no data for some of the outcomes stipulated in the protocol including costs and resource allocation. There were limited data for harms including anxiety and depression. There were also limited data for number of prenatal visits and admissions to the neonatal intensive care unit.

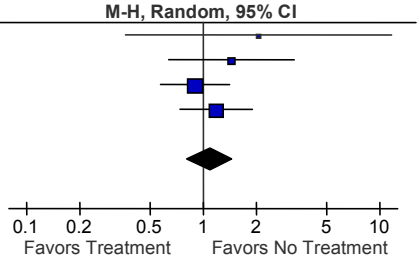
A single study (low risk of bias) assessed anxiety and depression using the Spielberger State-Trait Anxiety Inventory and the Edinburgh Postnatal Depression Score, respectively, 6 weeks after study enrollment and 3 months postpartum.[3] There was no significant difference between groups in anxiety at either time point, although there were significantly lower rates of depression in the treatment group at 3 months postpartum. Maternal stress in pregnancy has been associated with poor metabolic consequences in offspring, and the timing in gestation of the stress may be important.[5] Other research found that women with GDM compared with glucose-tolerant women had a higher level of anxiety at time of the first assessment; however, before delivery, these differences in anxiety scores did not persist.[6] Further research is required regarding the impact of a diagnosis of GDM on maternal anxiety and depression.

Four RCTs (one low risk of bias; three unclear risk of bias) reported small-for-gestational-age neonates and found no significant difference. This finding may have resulted from inadequate power to detect differences due to a small number of events; therefore, the finding of no significant difference should not be interpreted as equivalence between groups (Figure 1).

Figure 1. Effect of Treatment on Adverse Effects for Infants of Mothers With Gestational Diabetes Mellitus: Small-for-Gestational-Age Neonates

	Treatment		No Treatment			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bevier 1999[7]	3	35	2	48	3.0%	2.06 (0.36, 11.67)	
Bonomo 2005[8]	13	150	9	150	13.2%	1.44 (0.64, 3.28)	
Crowther 2005[3]	33	506	38	524	43.9%	0.90 (0.57, 1.41)	
Landon 2009[4]	36	477	29	455	39.9%	1.18 (0.74, 1.90)	
Total (95% CI)		**1,168**		**1,177**	**100.0%**	**1.10 (0.81, 1.48)**	
Total events	85		78				

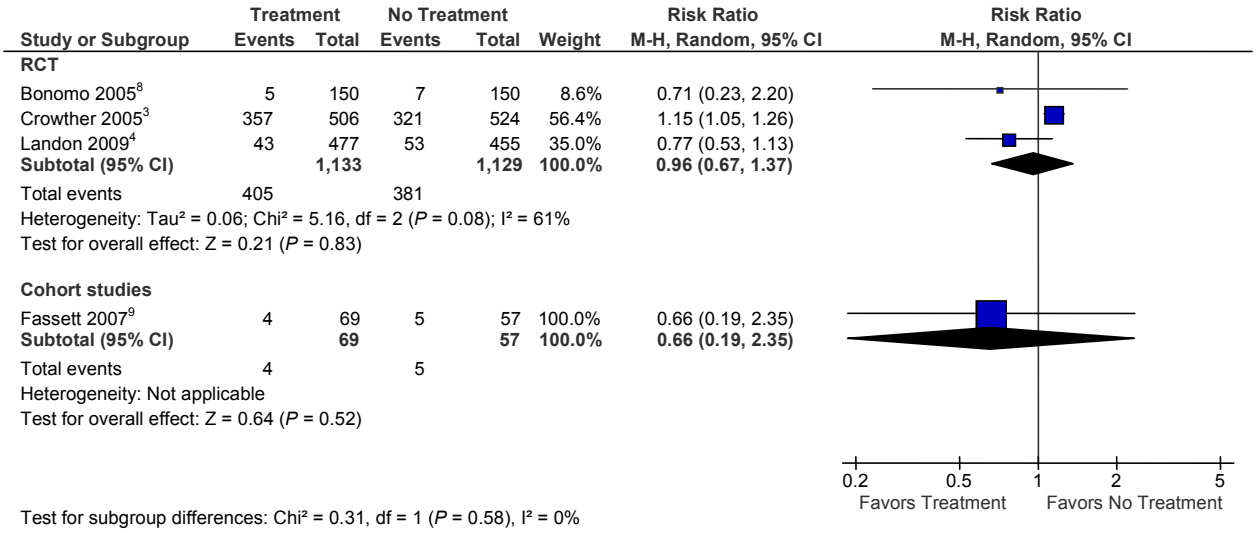
Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 3 (*P* = 0.62); I² = 0%
Test for overall effect: Z = 0.60 (*P* = 0.55)



CI = confidence interval.

In terms of healthcare resources, three RCTs (one low risk of bias; two unclear risk of bias) and one cohort study (good quality) provided data on admission to the neonatal intensive care unit and showed no significant differences overall (Figure 2). One trial conducted in Australia was an outlier, because it showed a significantly lower rate of neonatal intensive care unit admission in the no-treatment group. This difference may be attributable to site-specific policies and procedures, or differences in health provider remuneration between Australia and the United States. Two RCTs (one low risk of bias; one unclear risk of bias) reported on the number of prenatal visits and generally found significantly more visits among the treatment groups. Pooled analysis of these two RCTs showed no significant difference in the rate of induction of labor, although there was heterogeneity; one RCT showed significantly more inductions of labor in the treatment group,[3] whereas the other did not.[4] Different study protocols may account for the heterogeneity. In one study,[3] no recommendations were provided regarding obstetrical care, thus replicating usual clinical care of women with GDM. In the second, antenatal surveillance was reserved for standard obstetrical indications.[4]

Figure 2. Effect of Treatment on Adverse Effects for Infants of Mothers With Gestational Diabetes Mellitus: Neonatal Intensive Care Unit Admissions



CI = confidence interval; RCT = randomized controlled trial.

Although the evidence in this review did not identify substantial harms of treatment, the populations considered were those with mild GDM. There may be more precautionary management of women diagnosed with GDM who are perceived by clinicians to be at greater risk (e.g., those managed with insulin), which may result in unnecessary interventions (e.g., cesarean section).[10] Therefore, RCTs investigating the care of women diagnosed with GDM, including fetal surveillance protocols, are needed to guide obstetrical investigations and management of GDM. Furthermore, RCTs comparing delivery management for GDM with and without insulin or oral diabetes medications are needed to provide guidance on appropriate timing and management of delivery in women with GDM to avoid unnecessary interventions in "the real world" driven by healthcare provider apprehension over a label of GDM. The existing evidence does not allow a conclusion about how outcomes are affected by different diagnostic criteria. RCTs that randomize women to different glucose treatment targets are required.

References

1. Hillier TA, Vesco KK, Pedula KL, et al. Screening for gestational diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2008;148(10):766–775.

2. Langer O, Levy J, Brustman L, et al. Glycemic control in gestational diabetes mellitus—how tight is tight enough: small for gestational age versus large for gestational age? *Am J Obstet Gynecol.* 1989;161(3):646–653.

3. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

4. Landon MB, Spong CY, Thom E, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339–1348.

5. Phillips DI. Programming of the stress response: a fundamental mechanism underlying the long-term effects of the fetal environment? *J Intern Med.* 2007;261(5):453–460.

6. Daniells S, Grenyer BF, Davis WS, et al. Gestational diabetes mellitus: is a diagnosis associated with an increase in maternal anxiety and stress in the short and intermediate term? *Diabetes Care.* 2003;26(2):385–389.

7. Bevier WC, Fischer R, Jovanovic L. Treatment of women with an abnormal glucose challenge test (but a normal oral glucose tolerance test) decreases the prevalence of macrosomia. *Am J Perinatol.* 1999;16(6):269–275.

8. Bonomo M, Corica D, Mion E, et al. Evaluating the therapeutic approach in pregnancies complicated by borderline glucose intolerance: a randomized clinical trial. *Diabetic Med.* 2005;22(11):1536–1541.

9. Fassett MJ, Dhillon SH, Williams TR. Effects on perinatal outcome of treating women with 1 elevated glucose tolerance test value. *Am J Obstet Gynecol.* 2007;196(6):597.e1–4.

10. Buchanan TA, Kjos SL, Montoro MN, et al. Use of fetal ultrasounds to select metabolic therapy for pregnancies complicated by mild gestational diabetes. *Diabetes Care.* 1994;17(4):275–283.

Harms of Treatment of Gestational Diabetes Mellitus and Relationship to Diagnostic Threshold

Timothy Cundy, M.D.

Gestational diabetes mellitus (GDM) is currently defined as diabetes of onset or first recognition in pregnancy. This definition encompasses a wide range of dysglycemia: some women have previously unrecognized diabetes (usually type 2); some have prediabetes states; and the remainder have more modest, transient, pregnancy-related hyperglycemia. The risks to the fetus are clearly related to the degree of hyperglycemia: in women with GDM who have previously unrecognized type 2 diabetes, the rates of both perinatal mortality and major congenital malformations are the same as those in women with established diabetes antedating the pregnancy. With lesser degrees of hyperglycemia, the perinatal mortality and major congenital malformation rates in GDM are similar to the general population.[1,2] The current debate on diagnosing GDM centers on the degree of maternal hyperglycemia that is associated with less severe fetal and maternal outcomes, and the putative benefits of treating it. The proposal of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) to change the diagnostic criteria of GDM would mean significantly greater numbers of women would be diagnosed: in the United States, the proportion of pregnancies deemed to be affected would double or triple.[3] The expansion in numbers and the absence of clinical trial data demonstrating benefit in these low-risk pregnancies mean that their identification and treatment may turn out to be wasteful, useless, or even harmful. So what are the potential harms of the IADPSG approach?

Lack of Utility

The IADPSG recommendations were chosen by consensus, based on a particular set of glucose tolerance test-derived glucose values (level 5) observed in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.[3,4] Two of the four HAPO-defined “adverse pregnancy outcomes” are surrogate measures of debatable clinical significance (birth weight and cord C-peptide concentration). The dangers of overreliance on surrogate measures are well known,[5] so the clinical justification for the IADPSG approach relies on the relationship between the glucose tolerance test-derived glucose levels and the risk of neonatal hypoglycemia (almost identical for level 6 glucose values as for level 5) and the risk of cesarean section (which is confounded by maternal obesity[6]).

Proponents of the IADPSG approach point to clinical trials of the treatment of mild GDM that indicate that macrosomia, shoulder dystocia, and preeclampsia can be reduced.[7,8] However, these trials were conducted in women identified by two-stage testing and higher diagnostic criteria for GDM, so the benefits cannot be assumed to extend to the large number of women with milder hyperglycemia who would be identified by the IADPSG criteria. Most women with these pregnancy complications do not have GDM, so the overall impact is likely to be small.[4,9]

Accuracy of Diagnosis

The IADSPG proposal is that GDM can be diagnosed if any one of the fasting, 1-hour, or 2-hour blood glucose values on a 75-gram glucose tolerance test exceeds the recommended thresholds. Postload blood glucose measurements made on a glucose tolerance test are highly variable (with a coefficient of variation up to 20% on a 2-hour measure). In studies that

compared the results of women having two 100-gram glucose tolerance tests at short intervals, nearly a quarter of women changed diagnostic category on the second test—with a similar number going from abnormal to normal as the other way round.[10,11] Relying on a single blood glucose measurement to diagnose GDM means there is considerable imprecision and a high risk of overdiagnosis.

Overtreatment

When a woman acquires a diagnosis of GDM, it affects how obstetricians manage the pregnancy and makes them more likely to intervene, with earlier and more frequent induction of labor and therefore more operative deliveries. For example, in the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), the rate of induction of labor was higher in women in the intensive-care group; compared with the control group, more neonates required treatment with intravenous glucose and more suffered respiratory distress syndrome.[7] In the study of Naylor et al., the treatment of GDM normalized birth weights but did not affect the cesarean delivery rate, which remained high (33%), irrespective of whether macrosomia was present or absent.[12] It seems unlikely that diagnosing more women with GDM will in reality reduce the caesarean section rate, particularly in an environment where rates are increasing all around the world.

A meta-analysis of the treatment trials concluded that the only outcomes significantly affected by detection and treatment of mild GDM are a reduction in birth weight (by 100–140 grams, on average) and the incidence of shoulder dystocia.[13] Expanding the proportion of pregnancies diagnosed with GDM will inevitably lead to more treatment for mild hyperglycemia, lower maternal blood glucose levels (and more maternal hypoglycemia), slowed fetal growth, and thus the delivery of smaller babies.[14] Do all babies in women with mild GDM need to be made smaller, given the possible association of low birth weight with metabolic disorder in adulthood?[15]

Cost-Effectiveness

The sustainability of escalating healthcare costs is a major concern.[16] Identifying a substantially increased number of women with lesser degrees of hyperglycemia as having GDM would have a large impact on healthcare costs. A decision-tree model of the likely costs and utility of implementing the IADPSG proposal indicates that the incremental cost-effectiveness ratio (the amount we are willing to pay for each unit of improved quality of life) would be over $500,000 per quality-adjusted life-year.[17]

The strategy could only be cost effective if the later progression to type 2 diabetes was delayed or prevented,[17] but unfortunately there is no evidence that experiencing a GDM pregnancy does this. Women who have had GDM are often from deprived sections of the community and find it difficult to access care and adhere to lifestyle recommendations.[18,19]

Medicalization of Pregnancy

In both the large randomized controlled trials (ACHOIS and the Maternal-Fetal Medicines Unit Network study[7,8]), which used higher diagnostic criteria for GDM, women in the treatment groups had significantly more clinic visits than the control groups ($p<0.001$). Lowering the diagnostic threshold further so that nearly 20% of all pregnancies have GDM inevitably raises concerns about the further medicalization of pregnancies in asymptomatic women previously regarded as normal.[20] This is particularly so, given that interventions in the expanded group with

the mildest degree of hyperglycemia are of questionable value. In addition, there are potential long-term effects of maternal anxiety, the effects on future insurance costs, and medical follow-up.

References

1. Cundy T, Gamble G, Townend K, et al. Perinatal mortality in type 2 diabetes mellitus. *Diabetic Med.* 2000;17(1):33–39.

2. Farrell T, Neale L, Cundy T. Congenital anomalies in the offspring of women with type 1, type 2 and gestational diabetes. *Diabetic Med.* 2002;19(4):322–326.

3. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676–682.

4. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19): 1991–2002.

5. Yudkin JS, Lipska KJ, Montori VM. The idolatory of the surrogate. *BMJ.* 2011;343:d7995.

6. HAPO Study Cooperative Research Group. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study: associations with maternal body mass index. *BJOG.* 2010;117(5):575–584.

7. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

8. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339–1348.

9. Fadl HE, Östlund IK, Magnuson AF, et al. Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. *Diabetic Med.* 2010;27(4):436–441.

10. Harlass FE, Brady K, Read JA. Reproducibility of the oral glucose tolerance test in pregnancy. *Am J Obstet Gynecol.* 1991;164(2):564–568.

11. Catalano PM, Avallone DA, Drago NM, et al. Reproducibility of the oral glucose tolerance test in pregnant women. *Am J Obstet Gynecol*. 1993;169(4):874–881.

12. Naylor CD, Sermer M, Chen E, et al.; Toronto Trihospital Gestational Diabetes Investigators. Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? *JAMA.* 1996;275(15):1165–1170.

13. Horvath K, Koch K, Jeitler K, et al. Effects of treatment in women with gestational diabetes mellitus: systemic review and meta-analysis. *BMJ.* 2010;340:c1395.

14. Langer O, Levy J, Brustman L, et al. Glycemic control in gestational diabetes mellitus—how tight is tight enough: small for gestational age versus large for gestational age? *Am J Obstet Gynecol.* 1989;161(3):646–653.

15. Curhan GC, Willett WC, Rimm EB, et al. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation.* 1996;94(12):3246–3250.

16. Neumann PJ. What we talk about when we talk about health care costs. *N Engl J Med.* 2012;366(7):585–586.

17. Werner EF, Pettker CM, Zuckerwise L, et al. Screening for gestational diabetes mellitus: are the criteria proposed by the International Association of Diabetes and Pregnancy Study Groups cost-effective? *Diabetes Care.* 2012;35(3):529–535.

18. Kim C, Sinco B, Kieffer EA. Racial and ethnic variation in access to health care, provision of health care services, and ratings of health among women with histories of gestational diabetes mellitus. *Diabetes Care.* 2007;30(6):1459–1465.

19. Kieffer EA, Sinco B, Kim C. Health behaviors among women of reproductive age with and without a history of gestational diabetes mellitus. *Diabetes Care.* 2006;29(8):1788–1793.

20. Long H. Diagnosing gestational diabetes: can expert opinions replace scientific evidence? *Diabetologia*. 2011;54(9):2211–2213.

Economic Implications of Altering Gestational Diabetes Mellitus Diagnostic Criteria

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Gestational diabetes mellitus (GDM) is associated with numerous complications of pregnancy, including higher rates of preeclampsia, operative deliveries, macrosomia, shoulder dystocia, and birth injuries.[1] The Hyperglycemia and Adverse Pregnancy Outcome study demonstrated that hyperglycemia at levels below those diagnostic for GDM were associated with adverse maternal and neonatal outcomes.[2] Subsequently, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) convened a workshop conference in 2008 where it recommended using new cutoffs for the 2-hour oral glucose tolerance test in GDM screening and diagnosis.[3] In the United States, this would mean moving from a screening test followed by a diagnostic test to a single universal diagnostic test consisting of a fasting blood glucose followed by the 2-hour oral glucose tolerance test using a 75-gram glucose load. The adoption of these criteria is controversial. According to these criteria, an estimated 18% of patients would qualify for a diagnosis of GDM,[4] potentially adding to the costs of care for many pregnant women in the United States.

In addition to the impact on clinical outcomes that a change in the screening and diagnosis of GDM would bring, the economic impact of such changes needs to be considered as well. Increases in healthcare costs continue to outpace inflation.[5] In 2010, total expenditures on healthcare were estimated at greater than $2.5 trillion, or 17.9% of the gross domestic product, and are expected to rise to over $3 trillion and 20% of the gross domestic product by 2020–2025.[6,7] Thus, the short- and long-term costs of major changes in providing healthcare need to be incorporated into decisions about the provision of healthcare.

To compare the marginal benefits to be gained from new procedures, medications, and screening tests to their often increased costs, economic evaluations of such innovations are now commonly utilized.[8,9] These analyses may help guide healthcare providers, organizations, payers, professional societies, and policymakers to determine how and to whom particular healthcare services are provided.[10] The simplest economic analysis in healthcare takes into account only the costs. Such a *cost analysis* or *cost-only analysis* may be limited to just the direct costs of the provision of healthcare, or may be expanded to incorporate the indirect costs of patients' travel time and lost work productivity. A *cost-benefit analysis* makes a comparison between multiple programs or strategies on a purely financial level. In a cost-benefit analysis, all direct and indirect costs of healthcare are included as well as economic valuations of the outcomes. In this purely financial analytic tool, only economic distinctions are made between the value to society or individuals of having particular health outcomes.[11]

Although the term "cost-effectiveness analysis" is often used loosely to describe many types of economic analyses in healthcare, it specifically refers to an analysis in which costs and outcomes between two or more healthcare programs or strategies are compared. An incremental cost-effectiveness ratio is composed of a numerator, which is the difference between the costs of two programs, and a denominator, which is the difference between the outcomes of two programs. The denominator in a cost-effectiveness analysis can be any of a variety of outcomes, including the commonly used years of life saved (life-years), number of diagnoses made, and number of cases prevented. Within a particular clinical arena, these may all be reasonable outcomes to compare. However, comparisons between different fields of

medicine suffer from an “apples to oranges” problem. One way to compare disparate outcomes is by quality-adjusting the value of one’s life expectancy using utilities. *Utility* is the unit of value that some product or outcome, or in this case, health state, brings to an individual’s life. It is the common valuation given to consumption of goods and services in economics and is defined as ranging from 0 (no utility or death) to 1 (perfect happiness). Thus, in cost-effectiveness analyses, these valuations are defined as 0 for death and 1 for perfect health, with all other health states falling between these two. Once utilities are assigned to particular health states, they can be multiplied by the time spent in that particular health state to generate *quality-adjusted life-years.* When quality-adjusted life-years are used as the outcome measure in the denominator of a cost-effectiveness analysis, the analysis is considered a *cost-utility analysis*. An intervention is generally considered cost-effective if its incremental cost-effectiveness ratio is less than $100,000 per quality-adjusted life-year.

Thus, economic analyses of GDM diagnoses can utilize a wide range of analytic techniques and consider a wide range of costs. Short-term costs of GDM screening and diagnosis should consider the costs of screening tests, diagnostic tests, counseling of patients, time costs of providers and patients, blood glucose monitoring, and costs of complications of care related to preeclampsia, preterm birth, macrosomia, induction of labor, shoulder dystocia, cesarean delivery, neonatal hypoglycemia, and other short-term care costs. Long-term costs would include the downstream costs of being diagnosed with GDM in a current pregnancy on both the mother and child. These latter costs will be more difficult to estimate and more theoretical, but do hold merit for exploration.

Existing cost-effectiveness analyses have demonstrated a range of findings. First, the treatment of mild GDM has been demonstrated to be cost effective at $20,412 per quality-adjusted life-year.[12] In studies that examine the way in which GDM is screened and diagnosed, there is some range in the study findings. In one study, universal screening with the 1-hour glucose challenge test was found to be more cost effective than the 2-hour oral glucose tolerance test.[13] In another recent study, the costs of making the diagnosis of GDM with screening and diagnostic tests were compared, and the one-step 75-gram load test advocated by the American Diabetes Association (ADA) and IADPSG was the most costly.[14] However, two recent studies that consider not just the costs but effectiveness as well have both found that the ADA/IADPSG one-step test is cost effective when considering the benefits from diagnosis. One of the studies that incorporated downstream benefits to the risk of diabetes estimated an incremental cost-effectiveness ratio of $20,336 per quality-adjusted life-year.[15] The other study, which was more conservative and did not include downstream benefits regarding the prevention of maternal diabetes, found an incremental cost-effectiveness ratio of $61,503 per quality-adjusted life-year.[16] Although both studies suggest that the newly recommended format of diagnosing GDM is cost effective, they also estimate that there would be increased healthcare costs. In the first study, there would be an increase of approximately $5 billion in increased societal costs, whereas in the second study, this incremental increase in costs is estimated at approximately $500 million, assuming 4 million pregnant women each year in the United States.

There are a number of interesting issues to consider regarding the economic implications of screening for GDM and limitations of the existing studies. As noted, one of the studies screening with the 2-hour oral glucose tolerance test considered whether the likelihood of progression to type 2 diabetes mellitus was affected by receiving the diagnosis of GDM. Although one randomized controlled trial has shown benefit from an intervention to delay the onset of type 2 diabetes mellitus,[17] rates of postpartum glucose follow-up in patients with GDM is poor,[18] even despite an intervention involving intensive patient counseling to improve postpartum glucose

follow-up.[19] More information regarding this potential benefit needs to be generated before robust estimates can be applied with certainty.

These two most recent models depend on the effectiveness of GDM treatment in reducing rates of maternal and neonatal complications. Although such benefits of treatment were inferred from randomized controlled trials investigating the benefits of GDM treatment on patients with mild GDM so as to more accurately reflect a population with less severe hyperglycemia,[20,21] no current data exist that examine the benefits of GDM treatment on maternal and neonatal outcomes for patients who would be incrementally diagnosed with GDM under the new IADPSG guidelines. In addition, the utilities for many of the specific outcomes related to GDM have not been measured and need to be inferred from other related outcomes.

Another set of limitations involves the inability to estimate a number of costs related to GDM care. Such costs include those related to rates of antenatal admissions, effects on preterm birth, induction of labor, antenatal testing, some of the patient indirect costs, and of course the downstream costs of care. Future research in this arena should attempt to close the gap in knowledge to make societal and economically conscious decisions regarding GDM screening and diagnosis.

References

1. Hillier TA, Vesco KK, Pedula KL, et al. Screening for gestational diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2008;148(10):766–775.

2. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19): 1991–2002.

3. Metzger BE, Gabbe SG, Persson B, et al. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676–682.

4. Landon MB, Gabbe SG. Gestational diabetes mellitus. *Obstet Gynecol.* 2011;118(6): 1379–1393.

5. Chernew ME, Hirth RA, Cutler DM. Increased spending on health care: how much can the United States afford? *Health Aff (Millwood).* 2003;22(4):15–25.

6. Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group. National Health Care Expenditure Data. January 2012. Available at: http://cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/index.html. Accessed July 17, 2012.

7. Heffler S, Smith S, Won G, et al. Health spending projections for 2001–2011: the latest outlook. *Health Aff (Millwood).* 2002;21(2):207–218.

8. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med.* 1977;296(13):716–721.

9. Eisenberg JM. Clinical economics. A guide to the economic analysis of clinical practices. *JAMA.* 1989;262(20):2879–2886.

10. Cutler DM, McClellan M. Is technological change in medicine worth it? *Health Aff.* 2001;20(5):11–29.

11. Caughey AB, Kaimal AJ, Odibo AO. Cost-effectiveness of Down syndrome screening paradigms. *Clin Lab Med.* 2010;30(3):629–642.

12. Ohno MS, Sparks TN, Cheng YW, et al. Treating mild gestational diabetes mellitus: a cost-effectiveness analysis. *Am J Obstet Gynecol.* 2011;205(3):282.e1–7.

13. Poncet B, Touzet S, Rocher L, et al. Cost-effectiveness analysis of gestational diabetes mellitus screening in France. *Eur J Obstet Gynecol Reprod Biol.* 2002;103(2):122–129.

14. Meltzer SJ, Snyder J, Penrod JR, et al. Gestational diabetes mellitus screening and diagnosis: a prospective randomised controlled trial comparing costs of one-step and two-step methods. *BJOG.* 2010;117(4):407–415.

15. Werner EF, Pettker CM, Zuckerwise L, et al. Screening for gestational diabetes mellitus: are the criteria proposed by the International Association of the Diabetes and Pregnancy Study Groups cost-effective? *Diabetes Care.* 2012;35(3):529–535.

16. Mission JF, Ohno MS, Cheng YW, et al. Gestational diabetes screening with the new IADPSG guidelines: a cost-effectiveness analysis. *Am J Obstet Gynecol.* 2012; in press. [Epub ahead of print, July 2, 2012]

17. Ratner RE, Christophi CA, Metzger BE, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab.* 2008;93(12):4774–4779.

18. Stasenko M, Cheng YW, McLean T, et al. Postpartum follow-up for women with gestational diabetes mellitus. *Am J Perinatol.* 2010;27(9):737–742.

19. Stasenko M, Liddell J, Cheng YW, et al. Patient counseling increases postpartum follow-up in women with gestational diabetes mellitus. *Am J Obstet Gynecol.* 2011;204(6):522.e1–6.

20. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

21. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339–1348.

Practice Implications of Altering Gestational Diabetes Mellitus Diagnostic Criteria

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Potential implications of altering the diagnostic criteria for gestational diabetes mellitus (GDM) derive largely from two factors: (1) the logistics and practical aspects of administering the various screening and diagnostic tests, and, more importantly, (2) the significant increase in the resources needed to provide the additional care driven by a dramatic increase in the prevalence of GDM.[1]

At this time, most obstetric providers in the United States screen for GDM with a 50-gram glucose challenge test followed by a 100-gram glucose tolerance test if needed.[2] The 50-gram test is easily performed any time of the day in conjunction with a routine prenatal visit and does not require preparatory fasting. Although a small fraction of pregnant women can be identified with a prevalence of GDM so low as to preclude the need for testing, the American College of Obstetricians and Gynecologists has long recommended universal screening as a simpler method.[3] Depending on the cutoff value chosen for the 50-gram screen (130–140 mg/dL), between 14% and 23% of patients will require a second appointment for the 100-gram diagnostic test.[4] These patients are advised to pursue a normal diet for 2 or 3 days, must fast overnight and present to the clinic or laboratory the next morning, and remain for 3 hours following the glucose load. As a clinician, I must admit that there is some appeal to a simpler, one-step alternative. However, changing to the single-step, 75-gram 2-hour oral glucose tolerance test as proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) would require that all pregnant women arrive in the fasting state for the appointment during which the test was to be performed. With the common two-step method, only those patients who screen positive on the 50-gram test are required to do so. One small retrospective cohort study suggests that adopting the new IADPSG recommendations for screening and diagnosis would result in a 36% reduction in laboratory workload (time-based activity accounting) required for screening, but would increase the overall cost by 42%.[5] That study did not account for the increase in postpartum screening that would be expected by the increased prevalence of GDM.

The more dramatic and consequential implications for practice derive from the anticipated increase in workload and resources associated with an increase in the number of women identified with GDM by newer criteria. In 2008, hospital discharge data from the United States suggested a prevalence of GDM of 5.1% and an overall rate of diabetes of any type around 6.5%.[6] Relying on data from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial, if the diagnostic criteria recommended by the IADPSG were applied, 17.8% of all pregnant women would be diagnosed with GDM.[7] Authors for the HAPO group have demonstrated that applying the IADPSG criteria to the different centers participating in the trial resulted in significant regional variations in prevalence, ranging from 15.5% to 25.5% in participating U.S. sites.[8] Probably due to differences in the rates of obesity and abnormal glucose metabolism in different racial and ethnic groups, these variations suggest that any implications for practice, especially those of a logistic nature, also are likely to vary tremendously from one region to another.

To gain an appreciation of the practice implications driven by such a large increase in the prevalence of GDM, it is helpful to compare the typical prenatal care of pregnant patients with

and without the disorder. Upon the diagnosis of GDM, patients receive dietary instruction and the training needed to perform self-glucose monitoring. These tasks are usually accomplished in conjunction with a prenatal visit or scheduled separately, but always involve additional time spent by a healthcare provider. Additional prenatal care visits are typical and are intended to assess glucose control, determine any need for additional therapy, and increase surveillance of the health of the mother and fetus. Two randomized controlled trials (RCTs) have demonstrated that total visits with healthcare providers increase with treatment of glucose intolerance.[9,10] However, neither study accounted for antepartum surveillance for fetal well-being nor involved subjects with more than mild GDM. For GDM that is diagnosed at 26 to 30 weeks gestation, one can conservatively estimate two to four additional prenatal visits. Antenatal fetal testing is not recommended for women with diet-controlled GDM alone. However, about 25% of women with GDM (as currently diagnosed) will require medical therapy either with oral agents or insulin.[2] If insulin is needed, additional training is required, again in conjunction with a prenatal visit, or one scheduled separately. For patients with poor control and for those who require medical therapy, antepartum fetal testing is commonly initiated.[2,11] This is typically started around 32 weeks gestation and performed weekly or twice weekly with nonstress tests, biophysical profiles, or a combination of the two.[2] Relying on this description of common practices and assuming 4 million annual births in the United States, an increase in the prevalence of GDM to 18% has the potential to result in 450,000 more patient education visits, 1 million more clinic visits, and 1 million more antenatal fetal testing appointments annually.

To the extent that a diagnosis of GDM is associated with increased rates of induction of labor and cesarean section, a large increase in the prevalence of GDM would have significant implications for practice around the time of delivery. Simply identifying a patient as having GDM increases the risk of cesarean section. In a large prospective cohort study in which the treatment of GDM normalized birth weights, identifying a patient as having GDM significantly raised the risk of cesarean section even after adjusting for other factors.[12] There is little doubt that the risk of cesarean section increases with a clinician's perception of the risk of difficult delivery among patients with GDM, whether that risk is real or not.[13] Although RCTs have demonstrated a reduction in the risk of macrosomia with treatment of mild GDM, the effect of treatment on cesarean section rates has been inconsistent. In one RCT in which neither patients nor providers were blinded to GDM status, identification and treatment of mild GDM were associated with a 30% increase in the rate of induction of labor without a change in the rate of cesarean section.[9] In another trial, treatment of mild GDM was associated with no difference in the rate of induction of labor and a 20% reduction in the rate of cesarean section.[10] However, because clinicians in this trial were aware that patients in the treatment group had GDM and those in the control group might have untreated GDM, the results cannot be extrapolated to patients clearly identified as having GDM or not.

From a clinical perspective, the simplicity of a one-step approach as recommended by IADPSG is appealing. However, unless accompanied by significant changes in those clinical practices and interventions that are typically invoked by a diagnosis of GDM, the increase in prevalence associated with the new criteria would have dramatic implications for practice in the United States. These would include significant increases in clinic visits, antepartum fetal testing procedures, and interventions such as induction of labor and cesarean section. On the other hand, if improvements in outcomes such as macrosomia seen in recent treatment trials could be translated into more selective use of interventions such as cesarean section through changes in clinical practice, then expanding the diagnosis to a larger group of women would be more appropriate. Such changes in clinical practice should be informed by well-designed clinical trials comparing a population of women screened by the different criteria and managed by clinicians operating under strict clinical guidelines for intervention.

References

1. Flack JR, Ross GP, Ho S, et al. Recommended changes to diagnostic criteria for gestational diabetes: impact on workload. *Aust N Z J Obstet Gynaecol.* 2010;50(5): 439–443.

2. Landon MB, Gabbe SG. Gestational diabetes mellitus. *Obstet Gynecol.* 2011;118(6): 1379–1393.

3. American College of Obstetricians and Gynecologists Committee Opinion No. 504. Screening and diagnosis of gestational diabetes. *Obstet Gynecol.* 2011;118(3):751–753.

4. Coustan DR, Nelson C, Carpenter MW, et al. Maternal age and screening for gestational diabetes: a population-based study. *Obstet Gynecol.* 1989;73(4):557–561.

5. Agarwal MM, Dhatt GS, Othman Y. Gestational diabetes in a tertiary care hospital: implications of applying the IADPSG criteria. *Arch Gynecol Obstet.* 2012;April 7. [Epub ahead of print]

6. Wier LM, Witt E, Burgess J, et al. Hospitalizations related to diabetes in pregnancy, 2008. *Healthcare Cost and Utilization Project Statistical Brief #102*. Rockville, MD: Agency for Healthcare Research and Quality; December 2010. Available at: http://hcup-us.ahrq.gov/reports/statbriefs/sb102.pdf. Accessed June 18, 2012.

7. Metzger BE, Gabbe SG, Persson B, et al. Interational Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676–682.

8. Sacks DA, Hadden DR, Maresh M, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG Consensus Panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. *Diabetes Care.* 2012;35(3):526–528.

9. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

10. Landon MB, Spong CY, Thom E, et al. A multicenter randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339–1348.

11. American College of Obstetricians and Gynecologists Committee on Practice Bulletins. Gestational diabetes. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetricians-Gynecologists. Number 30. *Obstet Gynecol.* 2001;98(3):525–538.

12. Naylor CD, Sermer M, Chen E, et al.; Toronto Trihospital Gestational Diabetes Investigators. Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? *JAMA.* 1996;275:1165–1170.

13. Kjos SL, Schaefer-Graf U, Sardesi S, et al. A randomized controlled trial using glycemic plus fetal ultrasound parameters versus glycemic parameters to determine insulin therapy in gestational diabetes with fasting hyperglycemia. *Diabetes Care.* 2001;24(11):1904–1910.

Review of Maternal Experience of Having Diabetes Mellitus in Pregnancy

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The prevalence of gestational diabetes mellitus (GDM) has been dramatically increasing in the United States.[1–4] Diabetes in pregnancy raises the risk of later development of type 2 diabetes in both the mother and her children.[5–7] Despite the increasing prevalence of GDM and the increased risks associated with the prenatal condition, limited research has been published to date about the personal experience of women with GDM during pregnancy. Qualitative research studies such as those using a focus group methodology inform a deeper understanding of the maternal experience associated with this minimally explored area.

Recently, two qualitative studies were published, which included women with GDM. A phenomenological study using focus groups identified three primary themes: (1) feeling concern for the infant related to diabetes, (2) feeling concern for self related to diabetes, and (3) sensing a loss of personal control over their health. Subthemes for each of the primary themes also were identified including the sense of losing control.[8] Focus groups were used to identify perceived barriers to diabetes management, with distinction between women with pre-GDM and GDM. Identified barriers included (1) financial and access barriers, (2) barriers to diet and exercise, (3) communication difficulties, (4) lack of social support, and (5) barriers related to diabetes care.[9] There were overlapping themes between both studies such as issues of communication with healthcare providers, wherein women expressed their disappointment and frustration in difficulty with or lack of communication and access to information. Both studies demonstrated experiences of conflict as described by women in each of the studies: “I actually had to fight with all of my doctors…,”[9] and “I was constantly fighting….”[8] Women in both studies also expressed concern about problems with their infants as a result of having diabetes in pregnancy, as well as distress regarding the effort involved in diabetes self-management. A major difference between the studies was that one study found that the women were knowledgeable about their increased risk of developing type 2 diabetes later in life,[8] whereas the women in the other study demonstrated that they were not well informed.[9] Women participating in the focus groups by Nolan et al. were positive about the sharing of experiences in the focus group context and expressed the wish that such groups had occurred during their pregnancies.[8]

Prior to those two studies, there had been a few focus group studies that explored diabetes mellitus in pregnancy, although none had included women with GDM; yet certain consistent themes emerged that support the themes of the more recent qualitative studies of women with GDM. Qualitative studies of pregnant women with type 1 diabetes identified increased health challenges, lack of access to information and resources specific to diabetes in pregnancy, and a loss of control related to self-care.[10,11] Another study using focus groups and interviews examined the experience of women with pregestational, type 1, and type 2 diabetes. This study identified themes such as fear regarding the infant’s health, and frustration and disappointment in the increased emphasis on the diabetes aspect of their diabetic pregnancies.[12]

A review of these qualitative studies examining women’s experiences and perceptions of having diabetes in pregnancy points to the need for supportive, tailored care that addresses the biopsychosocial needs of women with diabetes in pregnancy. Based on the themes of the

qualitative studies, care of these women should demonstrate sensitivity to the increased concerns associated with having diabetes in pregnancy and respectful, nonjudgmental, clear, and informative communication regarding diabetes management, planning, and evaluation of care. As the women have consistently addressed the feelings of “loss of control,” efforts should be made by healthcare professionals to work collaboratively and respectfully with the women to establish realistic expectations for self-care including glycemic control. Support groups, either face to face or online for women with GDM with a healthcare professional serving as the group facilitator and respondent to questions could be offered as a means to share experiences, increase access to information, and encourage each other in their efforts.

Consistent themes have emerged through an analysis of the voices of women with GDM. These concerns need to be addressed in the healthcare system to optimize both maternal and fetal outcomes.

References

1. Dabelea D, Snell-Bergeon JK, Hartsfield CL, et al. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Screening Program. *Diabetes Care.* 2005;28:579–584.

2. Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. *Obstet Gynecol Clin North Am.* 2007;34:173–199.

3. Getahun D, Nath C, Ananth CV, et al. Gestational diabetes in the United States: temporal trends 1989 through 2004. *Am J Obstet Gynecol.* 2008;198(5):525.e1–5.

4. Metzger BE, Lowe LP, Dyer AR, et al; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New Engl J Med.* 2008;358(19):1991–2002.

5. Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care.* 2008;31(2):340–346.

6. Feig DS, Zinman B, Wang X, et al. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. *CMAJ.* 2008;179(3):229–234.

7. Retnakaran R, Qi Y, Sermer M, et al. Glucose intolerance in pregnancy and future risk of pre-diabetes or diabetes. *Diabetes Care.* 2008;31:2026–2031.

8. Nolan JA, McCrone S, Chertok IR. The maternal experience of having diabetes in pregnancy. *J Am Acad Nurse Pract.* 2011;23(11):611–618.

9. Collier SA, Mulholland C, Williams J, et al. A qualitative study of perceived barriers to management of diabetes among women with a history of diabetes during pregnancy. *J Women’s Health (Larchmt).* 2011;20(9):1333–1339.

10. Berg M, Sparud-Lundin C. Experiences of professional support during pregnancy and childbirth—a qualitative study of women with type 1 diabetes. *BMC Pregnancy Childbirth.* 2009;9:27.

11. King R, Wellard S. Juggling type 1 diabetes and pregnancy in rural Australia. *Midwifery.* 2009;25(2):126–133.

12. Lavender T, Platt M, Tsekiri E, et al. Women's perceptions of being pregnant and having pregestational diabetes. *Midwifery.* 2009;26(6):589–595.

Pro Status Quo

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In the early 1960s, O'Sullivan and Mahan established criteria for what is now recognized as gestational diabetes mellitus (GDM). Importantly, their statistically based criteria for the 100-gram oral glucose tolerance test were initially derived as an index of the subsequent risk to the mother of developing diabetes.[1] During the next several decades, it became evident that abnormal maternal glucose tolerance according to these criteria was associated with more immediate morbidity for both the mother and fetus. In 1979, the National Diabetes Data Group issued plasma glucose thresholds for this class of diabetes present only during pregnancy.[2] At around the same time, the First International Workshop-Conference on Gestational Diabetes Mellitus declared GDM a significant health risk that needed treatment.[3]

Status Quo

In the United States, the diagnosis of GDM currently relies on a two-step process including a 1-hour, nonfasting, 50-gram oral glucose screen followed, if positive, by a 3-hour, fasting, 100-gram oral glucose tolerance test. Although all pregnant women do not need to undergo a 50-gram screen, most obstetricians administer the screens universally as a practical matter. As is true for the glucose screen, there is more than one acknowledged set of thresholds for the diagnostic glucose tolerance test.[4] Women are typically diagnosed with gestational diabetes if two or more of the four values from the 100-gram test exceed chosen thresholds. However, because some women with only one abnormal value have an increased risk for adverse outcomes, some experts recommend that women with one abnormal value be identified and treated.[5]

These variations in diagnostic approach revolve around difficulties establishing the diagnosis in women with more minor degrees of glucose intolerance and make an exact description of the national status quo difficult. Nonetheless, the status quo on GDM screening is based on decades of study and can be generally described as a systematic two-step approach to identifying women who are at the highest risk for fetal overgrowth from maternal hyperglycemia. Despite this, in 2008, the U.S. Preventive Services Task Force concluded that current evidence was insufficient to assess the balance of benefits and harms to screening for GDM.[6]

Cause for Change

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated a continuous relationship between maternal glucose levels and increased birth weight/fetal hyperinsulinemia.[7] Glucose values from a 2-hour, 75-gram oral glucose tolerance test were stratified into seven categories at each of the three time points (fasting, 1 hour, and 2 hours). The likelihood of each outcome was then calculated using the first or lowest of these categories as the referent group for each time point. Recent randomized treatment trials, one from Australia and one from the United States, demonstrated reductions in fetal overgrowth and shoulder dystocia associated with treatment of GDM.[8,9] Rates of cesarean delivery were no different in one study and lower with treatment in the other. Although each study employed a different two-step diagnostic scheme for GDM, they are both considered justification for the current practices of screening and treatment of women with GDM. Bolstered by the results from these trials, the International Association of Diabetes and Pregnancy Study Groups (IADPSG)

used data from the HAPO study and recently recommended a universal single-step approach with a 75-gram test for screening and diagnosis of GDM.[10] Included in these recommendations were new glucose thresholds based on the arbitrary selection of a 1.75 odds ratio for large-for-gestational-age birth weight and fat or hyperinsulinemic babies. It is estimated that adoption of these guidelines would result in GDM being diagnosed in approximately 16%–18% of all pregnant women.[11] In other words, these recommendations will increase the prevalence of GDM in the United States threefold.

Evidence for Change

Despite the many years of study necessary to develop the status quo, there remains uncertainty surrounding the significance of mild GDM.[6] However, the recent intervention trials certainly provide strong evidence for treatment of women with mild GDM.[8,9] The proposed IADPSG recommendations will dramatically increase the number of women diagnosed with mild GDM, most of whom would be considered normal based on the approaches described in these trials. Therefore, it cannot be taken for granted that the benefits of treatment demonstrated in these two previous trials will be confirmed in the additional women identified using the approach recommended by IADPSG.[12] The inescapable fact is that there is currently no evidence of benefit to these newly diagnosed women. There is, however, some evidence that the mere labeling of women with the diagnosis may lead to an increase in the cesarean delivery rate.[13]

Cost of Change

In 2007, it was estimated that 180,000 (4.5%) women had GDM and delivered in the United States. Based on these numbers and assuming an average additional expenditure of $3,305 per pregnancy plus $209 in the newborn's first year of life, it was estimated that the annual national cost of GDM was $636 million.[14] If we adopted a change in diagnostic approach that would result in a threefold increase in women diagnosed with mild GDM, despite the small savings we might achieve by going to a single-step approach, it can be estimated that the annual national economic burden associated with GDM would increase to almost $2 billion. According to a recent cost analysis based on potential perinatal benefits, this dramatic cost increase could not be justified.[15]

Summary

Adopting the proposed IADPSG recommendations is premature for several reasons. Most importantly, there is absolutely no current evidence to demonstrate that identification and treatment of this new large number of women would result in any meaningful improvements in clinical outcome. When considering the decades of study necessary to establish benefit to the status quo, demonstrating benefit to treatment of lesser degrees of carbohydrate intolerance seems unlikely.[16] Secondly, the related increase in women diagnosed with mild GDM would most certainly impose a significant economic burden. Without evidence of benefit, this expenditure seems especially unwise at a time when healthcare resources are increasingly scarce. Finally, a single-step approach does not account for the variability in postload glucose measurements. The current two-step approach at least offers an opportunity to confirm the existence of significant glucose intolerance with a second test. In conclusion then, such an extraordinary shift in clinical practice without demonstrated benefit cannot be justified. Until such evidence exists, the status quo is preferred.

References

1. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes.* 1964;13:278–285.

2. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes.* 1979;28(12):1039–1057.

3. Freinkel N, Josimovich J. American Diabetes Association Workshop-Conference on Gestational Diabetes. Summary and recommendations. *Diabetes Care.* 1980;3(3):499–501.

4. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 30. Gestational diabetes. *Obstet Gynecol.* 2001;98(3):525–538.

5. Langer O, Brustman L, Anyaegbunam A, et al. The significance of one abnormal glucose tolerance test value on adverse outcome in pregnancy. *Am J Obstet Gynecol.* 1987;157(3):758–763.

6. U.S. Preventive Services Task Force. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2008;148(10):759–765.

7. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991–2002.

8. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

9. Landon MB, Spong CY, Thom E, et al. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339–1348.

10. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676–682.

11. Coustan DR, Lowe LP, Metzger BE, et al.; International Association of Diabetes and Pregnancy Study Groups. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. *Am J Obstet Gynecol.* 2010:202(6):654.e1–6.

12. Cundy T. Proposed new diagnostic criteria for gestational diabetes—a pause for thought? *Diabet Med.* 2012;29(2):176–180.

13. Naylor CD, Sermer M, Chen E, et al.; Toronto Trihospital Gestational Diabetes Investigators. Cesarean delivery in relation to birth weight and gestational glucose tolerance. *JAMA.* 1996;275(15):1165–1170.

14. Chen Y, Quick W, Yang W, et al. Cost of gestational diabetes mellitus in the United States in 2007. *Popul Health Manag.* 2009;12(3):165–174.

15. Werner EF, Pettker CM, Zuckerwise L, et al. Screening for gestational diabetes mellitus: are the criteria proposed by the International Association of the Diabetes and Pregnancy Study Groups cost-effective? *Diabetes Care.* 2012;35(3):529–535.

16. Ecker JL, Greene MF. Gestational diabetes—setting limits, exploring treatments. *N Engl J Med.* 2008;358(19):2061–2063.

Pro International Association of Diabetes and Pregnancy Study Groups

Boyd E. Metzger, M.D.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated strong, continuous associations of maternal glucose levels below those diagnostic of diabetes with birth weight, cord serum C-peptide levels, and newborn percentage of body fat, each >90th percentile. Significant associations were observed with primary cesarean delivery, clinically defined neonatal hypoglycemia, preeclampsia, and other measured outcomes. There were no obvious thresholds at which risks were increased.[1,2] The associations were independent of maternal age, body mass index, and family history of diabetes mellitus, and associations did not differ among 15 centers in nine countries. This provided an opportunity for global standardization of methods and criteria for the diagnosis of gestational diabetes mellitus (GDM). The HAPO study results were used by a consensus panel of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) to develop and publish recommendations for the diagnosis and classification of hyperglycemia in pregnancy.[3] Stepwise consideration of the HAPO study data led to the recommendation for threshold values for fasting plasma glucose and for 1-hour and 2-hour plasma glucose concentrations after a 75-gram glucose load of 5.1 (92), 10.0 (180), and 8.5 (153) mmol/L/mg/dL, respectively. These thresholds are the average glucose values at which odds for birth weight >90th percentile, cord C-peptide >90th percentile, and percentage of body fat >90th percentile reach 1.75 times the estimated odds of these outcomes at mean glucose values, based on fully adjusted logistic regression models. At least one of these thresholds must be equaled or exceeded to make a diagnosis of GDM. For the first time, diagnostic criteria are based on pregnancy outcomes. The two-step screening followed by diagnostic testing paradigm is replaced by a one-step test, and the requirement for only a single elevated value eliminates the quandaries associated with the finding of a single abnormal value under the current system. Laboratories will be able to standardize the glucose challenge in pregnancy and the nonpregnant state.

What frequency of GDM should we expect to find? It is generally assumed that the frequency with which GDM is detected is a reflection of the background population risk of type 2 diabetes mellitus. In 2010, 25% of the U.S. adult population had prediabetes and 11% had diabetes.[4] National Health and Nutrition Examination Survey data from 2005–2008 indicate that 4.5% of U.S. women age 18–44 had known or undiagnosed diabetes and 26.4% had prediabetes (impaired fasting glucose, impaired glucose tolerance) for a total of 30.9% with disorders of glucose metabolism (C. Cowie, National Institute of Diabetes and Digestive and Kidney Diseases, personal communication, September 2011). Thus, it is not unexpected that applying the IADPSG diagnostic thresholds to the HAPO study cohort (blinded participants plus those unblinded at the initial oral glucose tolerance test) shows a studywide frequency of GDM of 17.8%.[5] In centers where the diagnosis of GDM has required two abnormal test results, use of the IADPSG criteria can be expected to result in a substantial increase in numbers classified as GDM. However, the number diagnosed with GDM may not change greatly in centers that have applied the World Health Organization diagnostic criterion for GDM: namely, a 2-hour post-75-gram glucose load value of 7.8/140 (mmol/L or mg/dL), which is equivalent to impaired glucose tolerance in nonpregnant subjects.

In the development of the recommended diagnostic thresholds, the consensus panel took into consideration that some outcomes were related, some were relatively infrequent, and each oral

glucose tolerance test glucose measure (fasting, 1-hour, and 2-hour post-75-gram glucose load) was independently related to outcomes. The consensus panel based diagnostic thresholds on associations of glucose with outcomes that are pathophysiological components of diabetic fetopathy (birth weight, cord serum C-peptide concentration, percentage of newborn body fat >90th percentile) at odds ratios of 1.75 relative to odds at cohort mean glucose values.[3] As indicated in Table 1, the frequency of each HAPO study outcome is significantly greater in those with one or more glucose values at or above thresholds (GDM) than in those with all values less than threshold (non-GDM). For example, preeclampsia, birth weight, C-peptide, and percentage of newborn body fat >90th percentile are all twice as common in those with one or more glucose values at or above thresholds as in those with all values less than threshold. Preterm delivery, shoulder dystocia/birth injury, and cesarean delivery are approximately 40% more frequent than in those with all values less than threshold.

Table 1. Frequency of Outcomes When All Glucose Values Are Below Threshold or Any One or More Is Equal to or Above Threshold for Odds Ratio 1.75

Outcome	All Values < Threshold (%)	Any Value ≥ Threshold (%)*	Ratio	P
Birth weight >90th percentile	8.3	16.2	1.95	<0.001
Cord C-peptide >90th percentile	6.7	17.5	2.61	<0.001
Newborn percentage of body fat >90th percentile	8.5	16.6	1.95	<0.001
Preeclampsia	4.5	9.1	1.95	<0.001
Preterm delivery (<37 weeks)	6.4	9.4	1.47	<0.001
Primary cesarean delivery	16.8	24.4	1.45	<0.001
Shoulder dystocia and/or birth injury	1.3	1.8	1.38	<0.01
Clinical neonatal hypoglycemia	1.9	2.7	1.42	<0.01
Hyperbilirubinemia	8.0	10.0	1.25	<0.001
Intensive neonatal care	7.8	9.1	1.17	<0.01

*Threshold values are fasting plasma glucose ≥5.1 mmol/L (92 mg/dL), 1-hour 10.0 mmol/L (189 mg/dL), and 2-hour 8.5 mmol/L (153 mg/dL).

The HAPO study was an observational study, not a clinical trial; however, two randomized controlled trials (RCTs) comparing diagnosis and active treatment for mild GDM with standard obstetric care were conducted.[6,7] In both RCTs, treatment, primarily diet/lifestyle modification, resulted in reduced birth weight, a lower frequency of large-for-gestational-age births, and less preeclampsia or gestational hypertension. Glycemic values of participants were not identical in

the RCTs, and both were different than the HAPO observational study. However, there was substantial overlap between glucose values used for inclusion in the RCTs and the IADPSG recommended threshold values. For example, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS)[6] enrolled subjects whose median fasting plasma glucose was 4.8±0.6 mmol/L (86±11 mg/dL) and whose 2-hour 75-gram oral glucose tolerance test value was between 7.8 and 11.0 mmol/L (140 and 198 mg/dL), both lower than corresponding thresholds for the IADPSG GDM criteria. Furthermore, frequencies of outcomes such as large for gestational age or birth weight >90th percentile and preeclampsia in usual care versus treatment arms of the RCTs are similar to those observed in the HAPO study among women with one or more glucose values that meet or exceed the threshold, compared with those with all values below threshold (Table 1). Although not directly comparable, results of the two RCTS and findings in the HAPO study are complementary. It has been argued that very few of the pregnancies identified as having GDM by the proposed criteria will have adverse outcomes. Using data from the ACHOIS study, the number needed to treat to prevent one serious perinatal complication (death, shoulder dystocia, bone fracture, or nerve palsy) is 34, to prevent one case of preeclampsia is 17, and to prevent one case of macrosomia is 9.[6]

In some critiques of HAPO results and IADPSG recommendations, it has been suggested that efforts to reduce adverse pregnancy outcomes should be directed at obesity rather than GDM.[8–10] The HAPO study results have demonstrated independent associations of both GDM and obesity with pregnancy outcomes in circumstances where neither is actively treated.[11,12] GDM without obesity and obesity in the absence of GDM are independently associated with HAPO study outcomes. What is most striking is that the combination of GDM and obesity is strongly associated with each outcome. Although management of GDM requires strict glucose control, it results in lower frequencies of adverse outcomes. Optimal management of maternal obesity has yet to be defined.[13]

Although increasing the proportion of the pregnant population with GDM may increase healthcare costs, so does the epidemic of obesity and type 2 diabetes that we are currently experiencing. The challenge we all face is to develop approaches to treatment that prevent adverse outcomes but are more cost effective than current paradigms. The solution is not to ignore the epidemic of GDM that accompanies the epidemic of type 2 diabetes.

References

1. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New Engl J Med.* 2008;358(19):1991–2002.

2. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: associations with neonatal anthropometrics. *Diabetes.* 2009;58(2):453–459.

3. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676–682.

4. American Diabetes Association. Diabetes Statistics. Data from the 2011 National Diabetes Fact Sheet. January 26, 2011. Available at http://diabetes.org/diabetes-basics/diabetes-statistics/. Accessed July 7, 2012.

5. Sacks DA, Hadden DR, Maresh M, et al.; HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG Consensus Panel recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. *Diabetes Care.* 2012;35(3):526–528.

6. Crowther CA, Hiller JE, Moss JR, et al.; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477–2486.

7. Landon MB, Spong CY, Thom E, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361: 1339–1348.

8. Ryan EA. Diagnosing gestational diabetes. *Diabetologia.* 2011;54(3):480–486.

9. Long H. Diagnosing gestational diabetes: can expert opinions replace scientific evidence? *Diabetologia.* 2011;54(9):2211–2213.

10. Cundy T. Proposed new diagnostic criteria for gestational diabetes—a pause for thought? *Diabetic Med.* 2012;29(2):176–180.

11. HAPO Study Cooperative Research Group. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study: associations with maternal body mass index. *BJOG.* 2010;117(5):575–584.

12. Catalano PM, McIntyre HD, Cruickshank JK, et al.; HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care.* 2012;35(4):780–786.

13. Quinlivan JA, Julania S, Lam L. Antenatal dietary interventions in obese pregnant women to restrict gestational weight gain to Institute of Medicine recommendations: a meta-analysis. *Obstet Gynecol.* 2011;118(6):1395–1401.

Pro Alternative

Edmond A. Ryan, M.D.

Introduction

Recommendations for the detection of glucose intolerance during pregnancy should be evidence based, balance desirable and harmful effects, consider the perspective of the pregnant woman, and acknowledge implications for the mother and society. The present proposals have critical flaws: the traditional approach of the American College of Obstetricians and Gynecologists is not predicated on neonatal outcome evidence, and the new gestational diabetes mellitus (GDM) diagnostic criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) poorly predict large-for-gestational-age infants—the neonatal outcome of importance—and yet have major resource consequences. There is a better alternative.

Role of Glucose

Detection of glucose intolerance is important in both earlier and later pregnancy. In early pregnancy, women with undiagnosed type 2 diabetes mellitus have outcomes that are as dismal as if they had poorly controlled type 1 diabetes mellitus.[1] In later pregnancy, screening for GDM is important. Higher maternal glucose is associated with more large-for-gestational-age neonates and concomitant risks, and GDM in the mother is a forerunner of type 2 diabetes mellitus; moreover, offspring of women with GDM may be more obese or glucose intolerant.

Issues With Current Approaches

The traditional approach of the American College of Obstetricians and Gynecologists to the diagnosis of GDM is based on criteria stemming from values that predict later development of type 2 diabetes mellitus; it uses an abnormal 1-hour randomly timed glucose screen and then two values elevated on a subsequent 100-gram oral glucose tolerance test. Studies demonstrating benefit from treating GDM used such a two-step approach. This approach is not based on neonatal outcomes and involves a 3-hour oral glucose tolerance test with a 100-gram load of glucose that frequently causes nausea.

The IADPSG criteria use the evidence base from Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study data, then build on a consensus to treat glucose levels associated with a ≥1.75-fold increased risk of large-for-gestational-age infant, percentage of neonatal body fat, and elevated cord C-peptide and require just one abnormal value on a single oral glucose tolerance test. These criteria have not been used for prospective treatment studies; they involve every pregnant woman getting an oral glucose tolerance test—a test that at this level of glucose tolerance has only 60%–75% reproducibility[2]; they diagnose nearly a fifth of the pregnant population as having a disease needing intervention; and, finally, they are not cost effective without invoking the assumed prevention of later onset type 2 diabetes mellitus.[3] In terms of large-for-gestational-age infants, it is worth noting that increased maternal body mass index and gestational weight gain are also predictors of large-for-gestational-age infants.[4] Indeed, other factors are involved, because 78% of women in the HAPO study who delivered large-for-gestational-age infants had normal glucose tolerance by IADPSG standards and, in prospective studies, known metabolic factors account for only 26% of large-for-gestational-age infants.[5]

Given these, it is clear that maternal glucose has a role in large-for-gestational-age infants; maternal obesity is at least equally important but, even together, they do not account for most of what is responsible for large-for-gestational-age infants.

Alternative

There is an alternative approach that involves a 75-gram oral glucose tolerance test confirmation of the glucose abnormality and is convenient for the pregnant woman. The HAPO data indicate that the glucose values on the 75-gram oral glucose tolerance test associated with a *twofold* increased risk of large-for-gestational-age infants were 95, 191, and 162 mg/dL (5.3, 10.6, and 9.0 mmol/L) for fasting, and 1- and 2-hour postglucose load, respectively. In the HAPO study, any one elevated value was associated with large-for-gestational-age infants; thus a single raised value would suffice for diagnosis. Given reproducibility issues with the oral glucose tolerance test, some confirmation of a glucose abnormality is desirable—this could be achieved by universally using a 50-gram glucose screen with a cutoff of ≥140 mg/dL (7.8 mmol/L) to prompt an oral glucose tolerance test. Thus, such a two-step approach, when the oral glucose tolerance test is abnormal and there are abnormalities on two occasions (screen and oral glucose tolerance test), gives confidence that there is truly a problem with glucose tolerance. The National Institute of Clinical Excellence estimated that the two-step approach versus a single oral glucose tolerance test was nearly twice as preferable to pregnant women.[6]

One other issue is that if the glucose 1-hour post-50 grams was markedly elevated—for example, 350 mg/dL (19.4 mmol/L)—most would feel a confirmatory oral glucose tolerance test to be redundant, would assume GDM, and would treat. Thus there is a threshold above which one may presume the diagnosis of GDM is present. In diabetes practice outside of pregnancy, a value ≥200 mg/dL (11.1 mmol/L) is associated with the diagnosis of diabetes mellitus, prompting the use of this value as the cutoff for presumed GDM. Subsequent monitoring could confirm the elevated glucose. This approach is more cost effective and uses cutoffs similar to what is used in Canada, giving an 8% prevalence of abnormalities on the oral glucose tolerance test.[7]

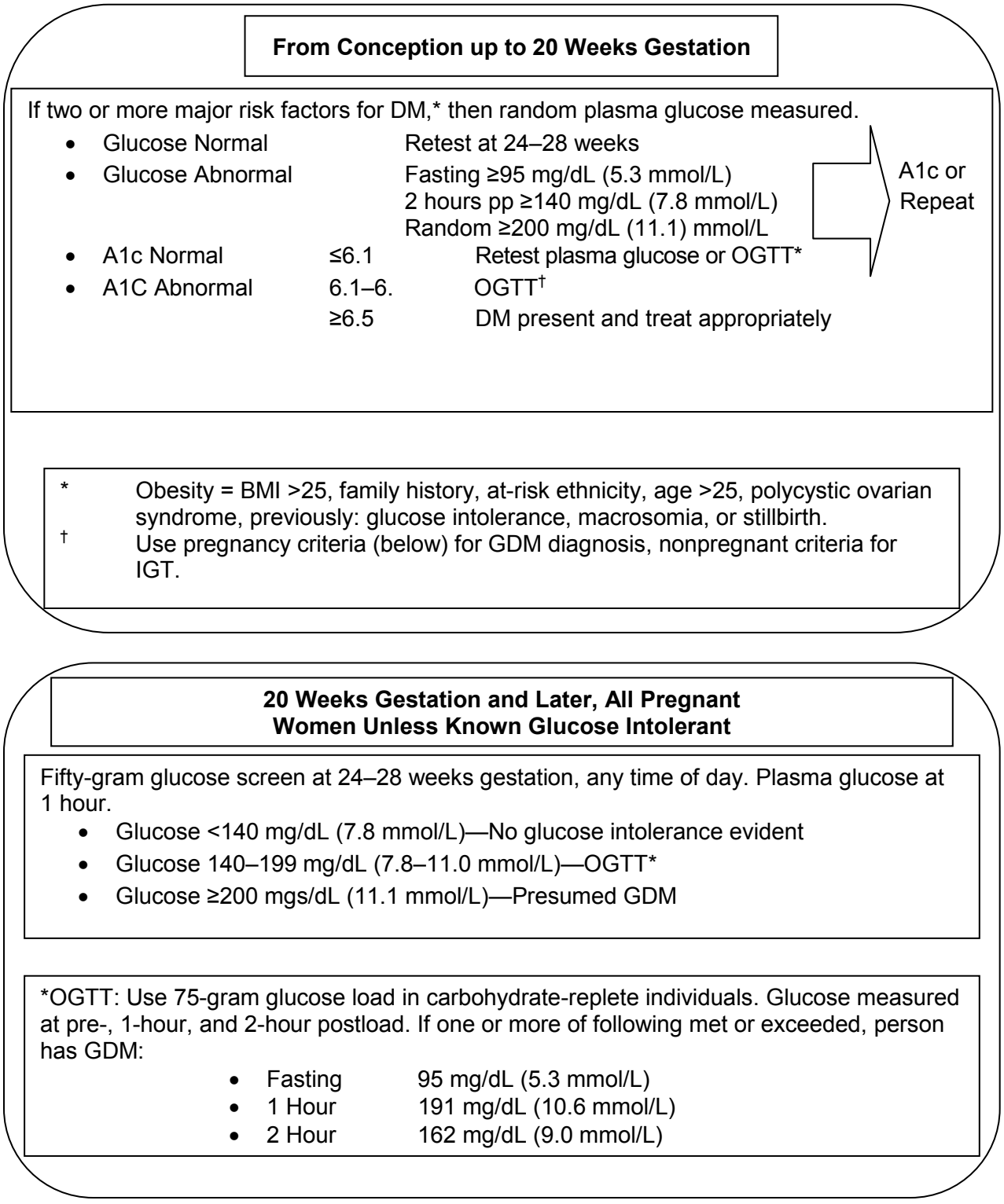
Summary

An alternative approach to defining glucose intolerance during pregnancy is shown in Figure 1. This approach is based on the need in early pregnancy to detect overt type 2 diabetes mellitus with its risk of a congenital malformation and poor outcomes, and in later pregnancy to detect GDM and its risk for large for gestational age and birth trauma. The oral glucose tolerance test glucose cutoffs are based on HAPO evidence linked to a twofold increased risk of large-for-gestational-age infants; women detected and treated will have less large-for-gestational-age infants and shoulder dystocia, and resource use is reasonable. The two-step approach is more patient acceptable and cost effective.

Conclusion

Maternal hyperglycemia is a treatable cause of large-for-gestational-age infants and thus is worth detecting; yet GDM accounts for only a minority of large-for-gestational-age infants, and maternal obesity must be considered a contributing factor. While we await the unravelling of the mechanisms of large-for-gestational-age infants, a balanced realistic approach to the diagnosis of GDM is needed. The alternative proposed here provides the two-step advantage of the

Figure 1. Detecting Glucose Intolerance in Pregnancy



BMI = body mass index; DM = diabetes mellitus; GDM = gestational diabetes mellitus; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.

traditional approach, and the evidence base from the HAPO study, and utilizes the concept of a presumptive diagnosis of GDM in the face of a very abnormal screen result. Areas needing further research attention are the lower and upper cutoffs for the 50-gram screen; whether the screen is better performed fasting, before noon, or at any time of the day; whether obesity management obviates the need to measure glucose; whether targeting glucose is the most pragmatic way to treat obesity during pregnancy; and the long-term consequence of maternal obesity or glucose intolerance on the offspring. Pending these studies, the alternative approach presented here is evidence based and provides a balance of harm and benefits.

References

1. Cundy T, Gamble G, Townend K, et al. Perinatal mortality in type 2 diabetes mellitus. *Diabetic Med.* 2000;17(1):33–39.

2. Balion CM, Raina PS, Gerstein HC, et al. Reproducibility of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) classification: a systematic review. *Clin Chem Lab Med.* 2007;45(9):1180–1185.

3. Werner EF, Pettker CM, Zuckerwise L, et al. Screening for gestational diabetes mellitus: are the criteria proposed by the International Association of the Diabetes and Pregnancy Study Groups cost-effective? *Diabetes Care.* 2012;35(3):529–535.

4. Catalano PM, McIntyre HD, Cruickshank JK, et al.; HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care.* 2012;35(4):780–786.

5. Retnakaran R, Ye C, Hanley AJ, et al. Effect of maternal weight, adipokines, glucose intolerance and lipids on infant birth weight among women without gestational diabetes mellitus. *CMAJ*. 1 May 22, 2012. Available at: http://cmaj.ca/lookup/doi/10.1503/cmaj.111154. Accessed June 17, 2012.

6. National Collaborating Center for Women's and Children's Health. Diabetes in Pregnancy: Management of Diabetes and Its Complications From Preconception and Its Complications to the Postnatal Period. National Institute of Clinical Excellence. Clinical Guideline 63. Table D.6. 2008; p. 170. Available at: http://nice.org.uk/nicemedia/live/11946/41320/41320.pdf. Accessed May 27, 2012.

7. Meltzer SJ, Snyder J, Penrod JR, et al. Gestational diabetes mellitus screening and diagnosis: a prospective randomised controlled trial comparing costs of one-step and two-step methods. *BJOG.* 2010;117(4):407–415.