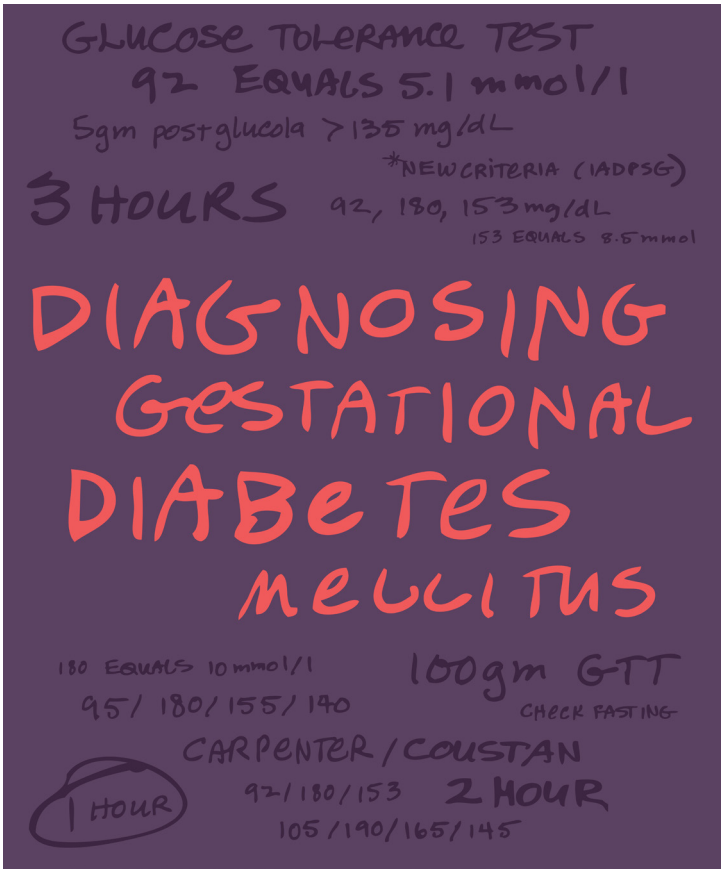
NIH Consensus Development Conference on
Diagnosing Gestational Diabetes Mellitus



NIH Consensus Development Conference Statements

Volume 29, Number 1
March 4–6, 2013

NATIONAL INSTITUTES OF HEALTH
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About the NIH Consensus Development Program

National Institutes of Health (NIH) consensus statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day. This statement is an independent report of the panel and is not a policy statement of NIH or the Federal Government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research, and that the information provided is not a substitute for professional medical care or advice.

Reference Information

Individuals who wish to cite this statement should use the following format:

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Disclosure Statement

All of the panelists who participated in this conference and contributed to the writing of this statement were identified as having no financial or scientific conflict of interest, and all signed forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH Consensus Panels are reviewed prior to selection to ensure that they are not proponents of an advocacy position with regard to the topic and are not identified with research that could be used to answer the conference questions.

For more information about conference procedures, please see ***http://prevention.nih.gov/cdp/about.aspx***.

Archived Conference Webcast

The NIH Consensus Development Conference: Diagnosing Gestational Diabetes Mellitus was webcast live March 4-6, 2013. The webcast is archived and available for viewing free of charge at ***prevention.nih.gov/cdp/conferences/2013/gdm/default.aspx***.

Abstract

Objective

To provide healthcare providers, patients, and the general public with a responsible assessment of currently available data on diagnosing gestational diabetes mellitus.

Participants

A non-U.S. Department of Health and Human Services, nonadvocate 15-member panel representing the fields of obstetrics and gynecology, maternal-fetal medicine, pediatrics, diabetic research, biostatistics, women's health issues, health services research, decision analysis, health management and policy, health economics, epidemiology, and community engagement. In addition, 16 experts from pertinent fields presented data to the panel and conference audience.

Evidence

Presentations by experts and a systematic review of the literature prepared by the University of Alberta Evidence-based Practice Centre, through the Agency for Healthcare Research and Quality (AHRQ). Scientific evidence was given precedence over anecdotal experience.

Conference Process

The panel drafted its statement based on scientific evidence presented in open forum and on published scientific literature. The draft statement was posted at http://prevention.nih.gov/ for public comment and the panel released a final statement approximately 10 weeks later. The final statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Conclusions

At present, GDM is commonly diagnosed in the United States using a 1-hour screening test with a 50-gram glucose load followed by a 3-hour 100-gram glucose tolerance test (a two-step approach) for those found to be abnormal on the screen. This approach identifies approximately 5% to 6% of the population as having GDM. In contrast, newly proposed diagnostic strategies rely on the administration of a 2-hour glucose tolerance test (a one-step approach) with a fasting component and a 75-gram glucose load. These strategies differ on whether a 1-hour sample is included, whether two abnormal values are required, and the diagnostic cutoffs that are used. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) has proposed diagnostic thresholds based on demonstrated associations between glycemic levels and an increased risk of obstetric and perinatal morbidities. The panel considered whether a one-step approach to the diagnosis of GDM should be adopted in place of the two-step approach. The one-step approach offers certain operational advantages. The current two-step approach is used only during pregnancy and is largely restricted to the United States. There would be value in a consistent, international diagnostic standard across one's lifespan. This unification would allow better standardization of best practices in patient care and comparability of research outcomes. The one-step approach also holds potential advantages for women and their healthcare providers, as it would allow a diagnosis to be achieved within the context of one visit as opposed to two. However, the one-step approach, as proposed by the IADPSG, is anticipated to increase the frequency of the diagnosis of GDM by twofold to threefold, to a prevalence of approximately 15% to 20%. There are several concerns regarding the diagnosis of GDM in these additional women. It is not well understood

whether the additional women identified by this approach will benefit from treatment, and if so, to what extent. Moreover, the care of these women will generate additional direct and indirect healthcare costs. There is also evidence that the labeling of these women may have unintended consequences, such as an increase in cesarean delivery and more intensive newborn assessments. In addition, increased patient costs, life disruptions, and psychosocial burdens have been identified. Available studies do not provide clear evidence that a one-step approach is cost-effective in comparison with the current two-step approach. After much deliberation, the panel believes that there are clear benefits to international standardization with regard to the one-step approach. Nevertheless, at present, the panel believes that there is not sufficient evidence to adopt a one-step approach. The panel is particularly concerned about the adoption of new criteria that would increase the prevalence of GDM, and the corresponding costs and interventions, without clear demonstration of improvements in the most clinically important health and patient-centered outcomes. Thus, the panel recommends that the two-step approach be continued. However, given the potential benefits of a one-step approach, resolution of the uncertainties associated with its use would warrant revision of this conclusion.

Introduction

Gestational diabetes mellitus (GDM) is a condition of carbohydrate intolerance of varying severity that begins or is first recognized during pregnancy, and is one of the most common complications of pregnancy. In some cases, GDM is actually type 2 diabetes that has not previously been diagnosed, but for most patients the glucose intolerance disappears soon after delivery. The prevalence of GDM varies because of different screening and diagnostic criteria, populations, race, ethnicity, age, and body composition. Using current testing criteria in the United States, GDM prevalence is estimated to be between 5% and 6%, affecting approximately 240,000 of the more than 4 million births occurring annually. Multiple studies have shown increases in GDM among diverse populations during the 1990s and early 2000s. This observed increase in GDM nationally is consistent with changes in known risk factors for GDM: advanced maternal age, family history of diabetes, higher body mass index, and changing racial and ethic demography. All of these risk factors have changed in the past 20 years in such a way as to increase the prevalence of GDM; for example, more than 20% of women in the United States are now obese as they enter pregnancy. Gestational diabetes mellitus is more common among certain ethnic groups, such as African American, Asian, Hispanic, and Native American women, compared with non-Hispanic white women, and recent patterns of immigration have led to increases in the numbers of many of these groups. These high-risk groups are not evenly distributed in the United States, leading to a disproportionate prevalence of GDM in different geographic regions.

Adverse short-term and long-term health outcomes for both the mother and her offspring have been associated with the diagnosis of GDM. For the mother, these outcomes include gestational hypertension (pregnancy-induced high blood pressure) and preeclampsia (high

blood pressure and proteinuria developed in pregnancy). The mother is also at increased risk for the later development of type 2 diabetes and other long-term metabolic complications, such as metabolic syndrome and cardiovascular disease. Excess glucose crosses the placenta and can cause adverse fetal effects. Fetal hyperinsulinemia (high levels of insulin in the blood) can lead to excess fetal size, with increased risks of shoulder dystocia (an impacted shoulder that requires additional obstetric manipulation during childbirth), cesarean delivery, respiratory distress syndrome, and neonatal metabolic complications.

At this time, most obstetric providers in the United States screen for GDM with a 50-gram glucose challenge test (GCT, measuring serum glucose 1 hour after a woman drinks a 50-gram oral glucose solution) followed by an oral 100-gram glucose tolerance test (OGTT, in which four blood samples are drawn over a 3-hour period after a woman drinks 100 grams of glucose solution) if the GCT result is abnormally high. This two-step approach has been recommended by the American College of Obstetricians and Gynecologists (ACOG). Depending on which GCT cutoff is chosen, 14% to 23% of patients will require the diagnostic OGTT.

Despite the near uniformity of current practice in the United States, a number of controversies remain: the value of routine screening, the most appropriate method (e.g., one-step compared with two-step), glycemic values on screening tests that are used to define “abnormal,” the number of abnormal values needed to make a diagnosis, and the effects of treatment on the short-term and long-term outcomes for women and their children. For example, in 2008, the U.S. Preventive Services Task Force (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.” At the same time, others support liberalizing the definitions, which would categorize

more pregnant women as having GDM. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) has proposed a one-step approach (fasting, 1-hour, and 2-hour glucose measurements), where GDM is diagnosed by only one abnormal value. Using their proposed cutoffs, this strategy is estimated to increase the number of women labeled as GDM twofold to threefold and could increase personal and societal costs. Therefore, clear evidence of substantive benefits from the IADPSG approach is needed to justify a change to that diagnostic technique.

The National Institutes of Health (NIH) Consensus Development Program is designed to address controversial questions of public health importance when there may be discordance between clinical practice and the available evidence. Consensus Development Conferences address targeted, carefully defined questions, which prompt a thorough review of the available evidence and solicit presentations from subject matter experts. An objective panel then concludes with a Consensus Statement, which addresses the critical questions.

By necessity, this panel, Diagnosing Gestational Diabetes Mellitus, cannot address every controversy surrounding GDM and focused on diagnosis. However, the panel is cognizant of the fact that most healthcare providers in the United States currently screen, and will continue to screen, for this condition. The panel also is aware that healthcare providers will continue to monitor and treat most patients based on whatever diagnosis of GDM is used, and that those will be expensive undertakings, with potentially negative consequences for those falsely categorized as having GDM. Although those facts have influenced deliberations, the panel concentrated on the diagnosis of GDM, not on the merits of routine screening or on issues of treatment and its effects. Simultaneously, the USPSTF will reexamine the issue of routine screening. In combination, the panel hopes to clarify an approach to GDM that may resolve key controversies.

To provide healthcare providers, public health practitioners, policymakers, and the general public with a comprehensive assessment of diagnosing GDM, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Nursing Research, Office of Research on Women's Health, Centers for Disease Control and Prevention, and the NIH Office of Disease Prevention convened a Consensus Development Conference on March 4–6, 2013, to assess the available scientific evidence. The panel included experts in the fields of maternal and fetal medicine, healthcare economics, obstetrics and gynecology, decision analysis and biostatistics, ethics, clinical pediatrics, diabetes education, epidemiology, neonatology, endocrinology, and a public representative. A Planning Committee developed seven questions to be addressed by the Consensus Development Panel:

1. 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?

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

3. 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?

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

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

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

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

During the first 2 days of the conference, experts presented information on each of the key questions. After weighing the scientific evidence—including the data presented by the speakers, input from attendees, and a formal evidence report commissioned through the Agency for Healthcare Research and Quality (AHRQ)—an independent panel prepared and presented a draft of this Consensus Development Conference Statement addressing the conference questions.

1. 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?

Testing for diabetes in pregnancy has been a routine part of obstetric practice since O'Sullivan published results for the OGTT in pregnancy more than 40 years ago. Currently, most practices use either a one-step or two-step approach for GDM diagnosis.

Two-step approaches, proposed by the National Diabetes Data Group (NDDG) and Carpenter and Coustan, are commonly used in the United States and involve the administration of a screening 50-gram GCT to the patient without regard to fasting (first step). If the plasma glucose level measured 1 hour after the load is less than a selected cutoff (usually 130 mg/dL, 135 mg/dL, or 140 mg/dL), the woman is considered GDM-negative, and no further testing is required. If the glucose level is greater than the cutoff, then a diagnostic test (second step) is needed to confirm the diagnosis of GDM. This second step involves a 100-gram oral glucose tolerance test (100-gram 3-hour OGTT) given while the patient is fasting; the fasting

1-hour, 2-hour, and 3-hour post-load glucose levels are measured and compared with recommended diagnostic criteria (Carpenter and Coustan or NDDG cutoffs) to confirm or reject the diagnosis of GDM (Table 1). The two-step approaches were not developed to diagnose diabetes in pregnancy per se, but rather to identify women at risk of developing diabetes mellitus later in life. Of note, the Canadian Diabetes Association uses a modified two-step approach that involves a 50-gram GCT with a diagnostic cutoff at 140 mg/dL (7.8 mmol/L), followed by a 75-gram 2-hour OGTT for the second step.

Table 1: Criteria and glucose thresholds for the diagnosis of GDM

Approach	Criteria*	Fasting mg/dL	1-hour mg/dL	2-hour mg/dL	3-hour mg/dL
Two-Step (100g load)	Carpenter and Coustan	95 (5.3mmo/L)	180 (10.0mmol/L)	155 (8.6mmol/L)	140 (7.8mmol/L)
	NDDG	105 (5.8mmol/L)	190 (10.6mmol/L)	165 (9.2mmol/L)	145 (8.0mmol/L)
	CDA	95 (5.3mmol/L)	191 (10.6mmol/L)	160 (8.9mmol/L)	
One Step (75g load)	WHO	126 (7.0mmol/L)		140 (7.8mmol/L)	
	IADPSG	92 (5.1mmol/L)	180 (10mmol/L)	153 (8.5mmol/L)	

* NDDG = National Diabetes Data Group; CDA = Canadian Diabetes Association; WHO = World Health Organization; IADPSG = International Association of Diabetes and Pregnancy Study Groups.

Single-step approaches proposed by the World Health Organization (WHO) and the IADPSG are commonly used outside of the United States to diagnose GDM. In the single-step approach, a 75-gram 2-hour OGTT is administered to the fasting woman. Using the WHO approach, fasting and 2-hour post-load glucose levels are measured, and using the IADPSG approach, fasting,

1-hour, and 2-hour glucose levels are evaluated against recommended criteria to confirm or refute the diagnosis of GDM. Table 1 summarizes the GDM diagnostic glycemic cutoffs for these criteria. Both the WHO and the IADPSG consider any single abnormal value as diagnostic of GDM, but the IADPSG consensus cutoffs are the only ones that are based on pregnancy outcomes (glucose values associated with a 1.75-fold increase in selected adverse pregnancy outcomes).

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

Patients

Adopting the IADPSG criteria would substantially increase the proportion of women diagnosed with GDM. Changing to a screening and diagnostic approach that requires every pregnant woman to undergo an OGTT is burdensome. In addition, the fasting state may be difficult and uncomfortable for some women. The diagnosis of GDM carries considerable inconvenience for patients, regardless of the criteria used. They must self-monitor their blood glucose levels several times a day and carefully monitor what they eat. They will need to meet with a registered dietitian, a diabetes educator, or both, resulting in additional appointments. Also (and despite a lack of clear efficacy), they often undergo fetal testing such as non-stress testing and additional obstetric ultrasonography. These extra procedures and provider visits require additional time and create additional challenges regarding transportation, child care, or employment and may result in additional out-of-pocket costs. These problems are likely enhanced for vulnerable populations.

Providers

Increasing the proportion of women with GDM by twofold to threefold has considerable implications for healthcare providers. Two randomized clinical trials have demonstrated that when additional women are diagnosed with GDM, the number of prenatal visits or visits to a healthcare provider increases. These visits would require additional clinical resources as well as the services of registered dietitians and diabetes educators. In one study of two large hospitals in Australia, it was estimated that the workload would increase approximately 30% if new diagnostic criteria for GDM were implemented. One estimate is that the IADPSG criteria would result in 450,000 more patient education visits, one million more clinic visits, and one million more prenatal testing appointments each year in the United States.

U.S. Healthcare Systems

The additional outpatient visits and testing described above will affect hospitals and payers. There may be capacity constraints relating to additional volume of laboratory testing. Other more difficult to quantify factors include increased responsibility on labor and delivery suites due to inductions of labor and increased time on postpartum rounds due to potentially more frequent cesarean deliveries.

In 2009, it was estimated that the annual cost in the United States for the care of GDM would increase from $636 million to $2 billion. Other published results suggest that direct medical and patient time costs would both be higher if the IADPSG protocol were adopted, even when accounting for the savings associated with the potential prevention of related complications. The results of economic analyses that weigh the tradeoff between costs, health benefits, and potential harms vary widely, and these analyses do not provide sufficient information to compare the various approaches likely due to

uncertainty regarding the health benefits of increased diagnosis of GDM. Cost-effectiveness analyses are more favorable to screening if it is assumed that screening leads to the prevention of future type 2 diabetes in women previously diagnosed with GDM. Long-term follow-up studies confirming this benefit, however, are lacking.

3. 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?

Many high-quality studies have evaluated maternal and fetal outcomes among women with untreated GDM compared with those without GDM. Although these studies employed various diagnostic criteria, several findings have been consistent. In terms of maternal outcomes, studies have shown that GDM increases risks of cesarean delivery, preeclampsia, and gestational hypertension. Studies also indicate increased risk for the later development of type 2 diabetes and other long-term metabolic complications.

In terms of fetal outcomes, methodologically strong studies have shown a continuous relationship between increasing glucose levels and increasing incidence of large-for-gestational-age infants and infants with macrosomia (a condition in which the newborn is significantly larger than average). In addition, a consistently higher risk of shoulder dystocia has been found among women with a diagnosis of GDM compared with those without; shoulder dystocia can lead to rare, but important, outcomes such as brachial plexus injury. Some studies report neonatal hypoglycemia

(low blood glucose) and hyperbilirubinemia (excess bilirubin in the blood) among neonates born to women with GDM, although the evidence supporting these associations has not been consistent. A relationship between GDM and subsequent childhood obesity has been found in some but not all studies. The effect on longer term outcomes in the offspring, including type 2 diabetes mellitus, is unclear. Of note, the maternal and fetal risks have been largely defined using the traditional two-step diagnostic approach for GDM. Milder forms of GDM diagnosed through other strategies may not be associated with these adverse outcomes to the same degree.

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated that the magnitudes of maternal and fetal risks increase with the severity of maternal hyperglycemia (high blood glucose). The HAPO study evaluated glucose tolerance at 24 weeks to 32 weeks during pregnancy in 25,505 pregnant women from 15 centers in nine countries, providing information on a heterogeneous, multinational, ethnically diverse group of women. For women with hyperglycemia during pregnancy that was not so severe as to require unmasking in order to inititiate treatment, i.e. plasma glucose levels greater than 105 mg/dL [fasting], greater than 200 mg/dL [2 hour], or greater than 160 mg/dL [random], increasing maternal glucose levels were related to increased infant birth weight, body fat, and cord C-peptide (a measure of insulin production in the infant) above the 90th percentile, and increased primary cesarean delivery rates. In addition, these women also had increased risks for premature delivery, preeclampsia, shoulder dystocia or birth injury, and hyperbilirubinemia. Neonatal hypoglycemia and admissions to neonatal intensive care units also were more common in infants born to mothers meeting the IADPSG criteria (used in the HAPO study) for GDM.

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

Very few well-designed, high-quality studies have attempted to estimate the benefit of treatment of GDM. These treatments included self-monitoring of blood glucose, medical nutrition therapy, and insulin in some patients. Criteria for the diagnosis of GDM varied, but two-step approaches were used in the two largest randomized trials. Women with more severe forms of GDM were not included in the studies.

Maternal Outcomes

Treatment of GDM reduced the risk for hypertensive disorders of pregnancy by approximately 40%. Shoulder dystocia risk was reduced with treatment by approximately 60%; however, as shoulder dystocia was a rare event, the absolute risk changed from only 3.5% (untreated) to 1.5% (with treatment). Another consistent finding among the studies was that the treatment of GDM did not increase the risk of cesarean delivery.

Results were not consistent among studies for maternal weight gain and risk for induction of labor; therefore, the panel could draw no conclusions on the effect of treatment on these two maternal outcomes. Evidence was absent or insufficient to conclude whether there is an effect of treatment of GDM on birth trauma, body mass index at delivery, or long-term maternal outcomes including type 2 diabetes mellitus, obesity, and hypertension.

Fetal, Neonatal, and Child Outcomes

A pooled meta-analysis of five randomized clinical trials found a 50% reduction in macrosomia in infants born to mothers who received treatment for GDM, although the absolute difference in mean birth weight was less than 150 grams in the two largest studies. Similarly, randomized trials have demonstrated that infants of mothers who received treatment for GDM were less likely to be large for gestational age (absolute risk reduction 6%). Randomized trials, however, have not shown a decrease in neonatal hypoglycemia in response to maternal treatment of GDM. There are no sufficient data available to conclude whether treatment of GDM modifies neonatal morbidities such as prematurity, admission to neonatal intensive care units, or mortality. More studies are needed to evaluate the long-term metabolic outcomes (obesity and risk of type 2 diabetes mellitus) of children born to women with GDM.

The panel strongly recommends caution when applying these results to clinical practice. First, participants in clinical trials typically are highly motivated individuals who are eager to adhere to even complex protocols in academic medical center venues with very favorable staff-to-patient ratios. These conditions are rarely present in the average clinical practice. Second, not all treatments employed in current daily practice were studied. Oral anti-diabetic agents, such as glyburide and metformin, are notably absent. Third, differing thresholds for criteria to diagnose GDM may change the size of the effect of the treatments for the entire group in unpredictable ways. Milder forms of GDM may not benefit from treatment. Finally, application of treatments purely for the sake of the benefits without regard for the costs would be inappropriate.

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

A potential harm of the increased diagnosis of mild GDM is patient anxiety. It is generally accepted that patients experience short-term stress and anxiety when receiving a new diagnosis of a serious condition, including GDM, which could adversely affect their health. Nonetheless, it is unclear if long-term stress and anxiety are increased. In part, this is due to a paucity of data. Also, it is possible that women may adapt to their diagnosis with diabetes management, thereby decreasing their anxiety level. In addition to anxiety, women with a new diagnosis of GDM have reported feelings of loss of control, shock, depression, fear, and disappointment.

Few studies directly addressed the emotional impact of screening for and diagnosis of GDM. One study noted a lower sense of well-being, less positive experience of their pregnancies, and more concern about their health. Another study noted that women with GDM had increased concern about their baby's health, and their own health, as well as a fear of losing personal control over their health. Also, the over-diagnosis of GDM may lead to the "medicalization of pregnancy," which transforms an otherwise normal pregnancy into a disease.

There is considerable variability in the 2-hour glucose tolerance test. Results may differ in as many as 25% of women if performed at different times. Thus, a one-step test is likely to result in more "false positive" results than a two-step test. In turn, positive tests will further increase cost, inconvenience, and anxiety.

The harms of medical therapy for GDM are well known. Medications such as insulin and oral hypoglycemic agents may cause hypoglycemia and other side effects. There are also obstetric "harms" associated with an increase in labeling patients with the diagnosis of GDM.

One randomized controlled trial has shown higher rates of induction of labor in women with GDM compared with normal controls. Women with GDM are more likely to undergo increased maternal and fetal monitoring. Subjective interpretation of ultrasound findings and fetal non-stress tests produces a high rate of false positives and unnecessary inductions of labor, failed inductions, and cesarean delivery. However, the literature has not yet addressed this possibility.

Cesarean rates may be higher in women with GDM, and it is uncertain whether treatment can mitigate this increase. Cesarean delivery is associated with a higher rate of short- and long-term complications. There is concern about the rising cesarean rate by many groups; the present rate in the United States is 32.9%. Since the vaginal-birth-after-cesarean rate is now less than 10%, most women, who delivered by primary cesarean, will again deliver by repeat cesarean. With each subsequent pregnancy, the rate of placenta previa (which occurs when a placenta partially or totally covers the mother's cervix) and placenta accreta (a serious pregnancy condition that occurs when blood vessels and other parts of the placenta grow too deeply into the uterine wall) increase dramatically. These conditions result in serious complications such as hemorrhage, infection, emergency hysterectomy, and even death.

A diagnosis of GDM may lead to more intensive neonatal care, potentially separating mother and infant. One study indicated that infants born to mothers with the diagnosis of GDM were more frequently admitted to an intermediate care nursery. (It is important to note that protocols for increased surveillance vary among hospitals.) Though there is theoretical risk for small-for-gestational-age fetuses in patients treated for GDM, the two largest randomized clinical trials have not confirmed this risk.

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

At present, GDM is commonly diagnosed in the United States using a 1-hour screening test with a 50-gram glucose load followed by a 3-hour 100-gram glucose tolerance test (a two-step approach) for those found to be abnormal on the screen. This approach identifies approximately 5% to 6% of the population as having GDM. The diagnostic threshold criteria for this test were originally predicated not on perinatal outcomes, but on the likelihood that a woman would develop diabetes mellitus in future years. More recently, evidence has accumulated that GDM identified by this system is associated with an increased risk of adverse maternal and perinatal outcomes.

In contrast, newly proposed diagnostic strategies rely on the administration of a 2-hour glucose tolerance test (a one-step approach). Each of these strategies is based on a one-step approach with a fasting component, a 75-gram glucose load, and 2 hours of testing. However, these tests differ on whether a 1-hour sample is included, whether two abnormal values are required, and the diagnostic cutoffs that are used. Most recently, the IADPSG has proposed diagnostic thresholds based on demonstrated associations between glycemic levels and an increased risk of obstetric and perinatal morbidities.

The panel considered whether a one-step approach to the diagnosis of GDM should be adopted in place of the two-step approach. The one-step approach offers certain operational advantages. The current two-step approach is used only during pregnancy and is largely restricted to the United States. There would be value in a consistent, international diagnostic standard across one's lifespan. This unification would allow better standardization of best

practices in patient care and comparability of research outcomes. The one-step approach also holds potential advantages for women and their healthcare providers, as it would allow a diagnosis to be achieved within the context of one visit as opposed to two.

To determine whether the advantages of the one-step approach should lead to its adoption, several criteria need to be fulfilled:

- There should be evidence that the additional women, who are identified by the one-step approach, have an increased frequency of maternal morbidities, perinatal morbidities, or both.
- There should be evidence that these morbidities, particularly among the new subset of women who are identified by the one-step approach but who would have been considered normal using the current two-step process, can be decreased by intervention.
- There should be evidence that the benefits of the decrease in morbidities outweigh the potential harms (maternal, perinatal, and societal).

While there is good evidence that increasing glycemic levels during pregnancy is associated with more maternal and perinatal morbidities, there is no single cutoff below which these associations are absent. These associations have been best demonstrated for the outcomes of shoulder dystocia, cesarean delivery, macrosomia, large-for-gestational-age birth weight, neonatal adiposity, neonatal hypoglycemia, and elevated umbilical cord blood C-peptide. It is not as clear whether associations exist for other important outcomes such as brachial plexus palsy, perinatal mortality, childhood obesity, or subsequent maternal metabolic complications.

There also is evidence that treatment of women with GDM, diagnosed either by the one-step or two-step approach, may improve some outcomes: macrosomia, large-for-gestational-age birth weight, shoulder dystocia, and hypertensive disease of pregnancy. Despite improvements in these intermediate outcomes, the frequencies of composite neonatal morbidity and cesarean delivery have not been consistently improved with treatment. Long-term outcomes for mothers and their offspring have not been improved in the few studies that have been performed.

The one-step approach, as proposed by the IADPSG, is anticipated to increase the frequency of the diagnosis of GDM by twofold to threefold, to a prevalence of approximately 15% to 20%. There are several concerns regarding the diagnosis of GDM in these additional women. There is insufficient evidence that the results of the published randomized clinical trials of treatment of mild GDM can be generalized to women who would be diagnosed with GDM by the IADPSG criteria. It is not well understood whether the additional women identified by this approach will benefit from treatment, and if so, to what extent. Moreover, the care of these women will generate additional direct and indirect healthcare costs. Such costs include increased utilization of registered dietitians and diabetes educators, prenatal care visits, and fetal assessments (ultrasonography and prenatal testing). There is also evidence in some studies that the labeling of these women may have unintended consequences, such as an increase in cesarean delivery and more intensive newborn assessments. In addition, increased patient costs, life disruptions, and psychosocial burdens have been identified. Therefore, available studies do not provide clear evidence that a one-step approach is cost-effective in comparison with the current two-step approach.

After much deliberation, the panel believes that there are clear benefits to international standardization with regard to the diagnostic approach to GDM. Nevertheless, at present, the panel believes that there is not sufficient evidence to adopt a one-step approach, such as that proposed by the IADPSG. The panel is particularly concerned about the adoption of new criteria that would increase the prevalence of GDM, and the corresponding costs and interventions, without clear demonstration of improvements in the most clinically important health and patient-centered outcomes. Thus, the panel recommends that the two-step approach be continued. However, given the potential benefits of a one-step approach, resolution of the uncertainties associated with its use would warrant revision of this conclusion.

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

The panel identified the following research needs for GDM diagnosis:

- Develop an approach to diagnosis in the United States that is more consistent with international diagnostic approaches. However, before adoption of a new approach, further research is required to define the optimal strategy that will improve health in the most cost-effective manner. For example, one could evaluate the diagnostic thresholds associated with an odds ratio for adverse outcomes of 2.0 in the HAPO study (as opposed to the odds ratio of 1.75 that is currently recommended by the IADPSG). This strategy would have the dual advantages of being based on important clinical outcomes and of utilizing the single-step, 75-gram 2-hour approach that is widely used internationally, while avoiding an increase in the prevalence of GDM.

- Determine whether the additional women categorized as having diabetes by the IADPSG model, who would be considered normal in the two-step strategy, accrue significant benefits from treatment. This question may be best answered by a randomized controlled trial that, ideally, would use clinically important health and patient-centered outcomes.
- Conduct cost-benefit, cost-effectiveness, and cost-utility analyses to more fully understand the resource implications of changing the thresholds for a diagnosis of GDM.
- Given that the different approaches represent different burdens for patients, conduct research to understand patient preferences and the psychological consequences of the diagnosis of GDM.
- Perform well-conducted prospective cohort studies of the "real world" impact of GDM treatment on care utilization and practice patterns.
- Assess lifestyle interventions during pregnancy, such as nutrition and exercise, that may improve maternal and fetal outcomes in women with GDM. Consider factors, other than GDM (e.g., obesity), that contribute to fetal macrosomia in order to develop a risk model for macrosomia.
- Assess the long-term impact that a label of GDM may have for future pregnancy planning, future pregnancy management, and future insurability.
- Conduct further study of the long-term metabolic, cardiovascular, developmental, and epigenetic (inherited changes in phenotype [appearance] caused by mechanisms other than changes in DNA) impact on offspring whose mothers have been treated for GDM.

- Assess interventions to decrease the subsequent risk of the occurrence of metabolic syndrome, diabetes, and cardiovascular disease in women with GDM.

Footnote: While we do not believe that current evidence justifies a departure from the current two-step approach to screening and diagnosis, we do believe that a single standard both for screening (130 mg/dL, 135 mg/dL, or 140 mg/dL for the GCT) and for the diagnostic thresholds on the GTT (Carpenter and Coustan or NDDG) should be adopted by appropriate professional organizations.

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