The diagnostic criteria for gestational diabetes: to change or not to change?

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In William Shakespeare’s perhaps most famous play, the protagonist (Hamlet) contemplates the nature of action versus inaction. His dilemma is whether or not he should act against what he thinks is wrong or to just ignore the situation and hope it goes away. Sometime next year, the National Institutes of Health (NIH) Office of Disease Prevention (ODP) will be faced with a quandary not unlike Hamlet’s: to change or not to change the diagnostic guidelines for gestational diabetes mellitus (GDM).

The different diagnostic methods for detecting and diagnosing GDM being employed around the globe today have led several groups to call for the universal adoption and implementation of a single diagnostic and screening strategy. This proposed new strategy would include changing from a 2-step to a 1-step screening process, along with a lower glucose threshold for the diagnosis of GDM. ODP has convened this consensus development conference in an attempt to better understand the potential ramifications of changing the current screening and diagnostic criteria for GDM vs keeping current practices in place. Thus, their question is indeed: to change or not to change?

NIH consensus statements are the result of several intensive days of plenary sessions, in which invited expert speakers present the most up-to-date research on a particular topic, followed by town hall fora in which speakers, panelists, and the general public in attendance openly discuss the pros and cons of each argument. Thus, these consensus statements represent the findings and opinions of the conference participants and not those of the NIH. Indeed, NIH does not have the authority to issue clinical guidelines, and the recommendations that result from these consensus conferences may or may not be adopted by professional organizations and experts.

There is growing evidence that elevated plasma glucose concentrations, or hyperglycemia, below what is currently considered GDM are pathologic to fetuses. Thus, many clinicians have called for adopting a more aggressive approach to screening and diagnosing GDM, not only in this country, but worldwide. Based on such evidence, it is the hope of some in the field of diabetes in pregnancy that this NIH consensus conference will spur the immediate adoption of a universal, 1-step screening process and a lower diagnostic threshold for GDM. Others in the field, including the American College of Obstetricians and Gynecologists, have reviewed the available scientific evidence and expressed a reluctance to see current practices changed because they believe there is not yet sufficient evidence to prove that such a change would lead to better maternal or newborn outcomes.

Although the calls for change do have many merits, research suggest that lowering the diagnostic threshold for GDM will significantly increase the number of cases of GDM diagnosed. Many women diagnosed with GDM seek care or consultation with a maternal-fetal medicine specialist. If significantly more
women are being diagnosed with this illness, such an increase is likely to have an impact not only on the practice of general obstetricians, but it also may create medicolegal liabilities for those general obstetricians who choose to manage GDM patients themselves.

Thus, we believe that in order for the consensus conference participants to support changing current clinical practice for GDM, they must be fully prepared to address, in addition to the science, the public health policy, physician practice, and economic implications of such a change, including:

- How will we cope with the additional health care personnel needs for these newly diagnosed patients?
- How much will it cost to significantly increase the number and incidences of GDM and who will absorb those added costs?
- Is there a treatment that can improve outcomes with the new thresholds?
- What are the practice and legal implications for the physicians caring for pregnant women, if this change leads to overdiagnosis of GDM?

In deciding whether to change or not to change current practice, consensus conference participants must decide which course of action they will recommend. However, unless there are sufficient data to address these types of issues, it may not be possible to reach consensus on whether or not to change current clinical practice for diagnosing and screening GDM at this juncture. In the absence of data to address the aforementioned questions, we may need to wait until additional studies are completed to know which course of action to take.

The fetal and maternal consequences of GDM

The United States has the highest known incidence of GDM in the world, with as many as 7%, or 200,000, of pregnancies diagnosed with GDM each year.12 There is an accompanying high incidence of maternal and fetal morbidity associated with GDM, which is discussed below.

Fetal consequences

Uncontrolled maternal GDM exposes the fetus to an abnormal glucose load, leading to a compensatory increase in fetal insulin secretion. The resulting hyperinsulinemia often leads to excess fetal growth, and these large-for-gestational age (LGA) fetuses face a significantly increased risk for morbidity at the time of vaginal birth, such as shoulder dystocia, brachial plexus injury, and newborn asphyxia.14,15 Consequently, most obstetricians prefer to deliver LGA infants via cesarean section. Fetuses exposed to a high intrauterine glucose environment also have elevated risks for a number of other complications upon delivery, including neonatal respiratory distress syndrome, cardiomyopathy, hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, and hyperviscosity.16

In 2008, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study,17 which followed the birth outcomes of approximately 25,000 pregnant women at 15 centers, reported that subclinical hyperglycemia was independently associated with LGA births and increased cord plasma serum C-peptide levels. The HAPO study also found weaker, but still significant, associations with neonatal hypoglycemia and primary cesarean delivery. Other investigators have reported that children born to mothers with GDM have nearly double the risk of developing childhood obesity and/or metabolic syndrome compared children born to non-diabetic mothers.18-21

Maternal consequences

A number of studies also have shown that GDM can have adverse health consequences for the mother.21-24 Indeed, women with a history of GDM and obesity have a greater risk of developing metabolic syndrome than mothers with no such history.20,23,24 GDM also has been found to be a leading risk factor for women who subsequently develop hypertension,22 type 2 diabetes,23 and obesity.15,21

Mechanisms

How GDM causes maternal and fetal morbidities is still unclear. Research suggests, however, that maternal gestational hyperglycemia and subsequent fetal hyperinsulinemia may predispose offspring to increased adiposity, impaired glucose tolerance, hyperinsulinemia, and insulin resistance.25 Women with GDM also have been shown to have fewer circulating progenitor cells at 24–32 weeks’ gestation and 1–2 days postpartum compared to controls.26 Because the normal physiologic increase in circulating progenitor cells during pregnancy is impaired in women with GDM, it is believed that this impairment may contribute to endothelial dysfunction and GDM-associated morbidities in mothers and infants. Ethnicity27,28 and vitamin D deficiency29 also have been shown to be associated with an increased risk for GDM-related morbidities. In addition, several recent studies have suggested that maternal pre gravid body mass index is associated with adverse maternal and fetal outcomes independent of diabetes or elevated plasma glucose concentrations.30-32

The evolution of a diagnostic controversy

Since the 1970s, the standard test for diagnosing GDM in the United States has been a 2-step screening approach, which uses a 50-g glucose challenge test (GCT) followed by a 100-g, 3-hour oral glucose tolerance test (OGTT).24 The current screening threshold for GDM in the United States is ≥140 mg/dL on the 50-g, 1-hour oral GCT. Those who screen positive are given a 100-g oral glucose load, and their plasma glucose concentration typically is measured 2 or 3 hours later. GDM is officially diagnosed with a positive result on ≥2 OGTTs. The current diagnostic thresholds for the OGTT are: ≥180 mg/dL (1 hour); ≥155 mg/dL (2 hour); and ≥140 mg/dL (3 hour).10

These thresholds are based on landmark work by O’Sullivan and Mahan33 and O’Sullivan et al34 in the late 1960s and early 1970s and, subsequently, Carpenter and Coustan35 and Coustan et al.36 Outside the United States, however, the most common strategy for diagnosing GDM for many years has utilized a 1-step, 75-g OGTT. This approach, which holds that a single positive OGTT is diagnostic of GDM, was endorsed by the World Health Organization in 1999.37
As early as the 1980s, based on their observations of adverse birth outcomes among women with subclinical hyperglycemia during pregnancy, Carpenter and Coustan35 and Coustan et al46 began suggesting that thresholds for GDM diagnosis should be set below the O’Sullivan and Mahan thresholds. More recently, others have proposed that the glucose tolerance test (step 1) be eliminated and that GDM diagnosis should be universally based on a single abnormal value on the 1-step, 75-g OGTT.

The previously mentioned HAPO study17 followed up on these and other observations by utilizing the 1-step, 75-g OGTT to diagnose GDM in a large cohort of pregnant women. The HAPO study identified a strong, continuous association between adverse birth outcomes and maternal glucose concentrations below those typically diagnostic of diabetes. Based on these findings, in 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended changing the current GDM screening method used in the United States to the 1-step, 75-g OGTT and lowering plasma glucose thresholds for the diagnosis of GDM: fasting plasma glucose ≥92 mg/dL; 1-hour plasma glucose ≥180 mg/dL; and 2-hour plasma glucose ≥152 mg/dL. The IADPSG recommendations recently were endorsed by the American Diabetes Association (ADA) and are currently under review by other organizations in the United States.40

A key argument for changing the current diagnostic guidelines for GDM in the United States is that a single diagnostic test—by eliminating the screening phase—will be more convenient for the provider and the patient. Furthermore, because it is more user-friendly, it is argued that the 1-step diagnostic test also will be much easier to administer and, thus, the earlier diagnosis and treatment of GDM will lead to more consistent care, better organized GDM research, and, ultimately, better outcomes for mothers and their babies.8

Several recent studies suggest that the lower diagnostic threshold will result in medical costs savings. For example, Ohno et al41 investigated the cost-effectiveness of treating mild GDM and found, overall, that it is cost-effective in terms of improving maternal and neonatal outcomes including decreased rates of preeclampsia, cesarean sections, macrosomia, shoulder dystocia, permanent and transient brachial plexus injury, neonatal hypoglycemia, neonatal hyperbilirubinemia, and neonatal intensive care unit admissions. A follow-up study by the same group42 found that screening pregnant women at 24–28 weeks’ gestational age under the new IADPSG guidelines with the 2-hour OGTT is cost-effective in improving maternal and neonatal outcomes but noted that questions about how the health care system will provide expanded care to this group of women will need to be examined.

Indeed, there are those who argue that implementing the IADPSG recommendations will have major adverse consequences for an already strained US health care workforce.43,44 It has been estimated that lowering the diagnostic plasma glucose thresholds, as recommended by the IADPSG, will increase the number of women diagnosed with GDM each year by almost 3-fold vs the previous ADA recommended criteria (37.7% vs 12.9%).11 Consequently, the US health care system will be challenged with the addition of potentially tens of thousands of women newly diagnosed with GDM at a time when recent health care reforms already are increasing the demand for physician and nursing services.

Already, the critical shortage of primary care clinicians in this country is being called a “national disaster” by some in the public health community.45 Demand for physician services will increase by an estimated 25% during the next decade, and there will be a national shortage of >400,000 nurses over that same period.45

Research suggests that adopting IADPSG recommendations will entail not only a significant increase in the number of primary health care providers but also in their workload, as they may have to provide more intensive preconception and follow-up postnatal care for this group of patients. Werner et al46 for example, analyzed the cost-effectiveness of 3 GDM diagnostic strategies: (1) no screening; (2) current screening practice (1-hour, 50-g GCT between 24–28 weeks, followed by 3-hour, 100-g glucose tolerance test when indicated); or (3) the screening practice proposed by the IADPSG. They found that IADPSG recommendations are cost-effective, but only when women diagnosed with GDM received additional prenatal monitoring to mitigate the risks of preeclampsia, shoulder dystocia, and birth injury. Postdelivery counseling and behavior modification to reduce patients’ future diabetes risks also were key to the cost-effectiveness of the lower diagnostic threshold in this study.

Others have expressed concerns that adopting the new diagnostic criteria for GDM will unnecessarily label many women with mild levels of hyperglycemia as being diabetic and at high risk for adverse consequences, especially if diagnosis is based on a single test.47 Kalter-Leibovici et al48 analyzed data from the Israeli HAPO study participants (n = 3345) to study the implications of implementing the IADPSG recommendations for screening and diagnosing GDM in Israel. They calculated adverse outcome rates and compared them for women who were positive according to: (1) IADPSG criteria; (2) IADPSG criteria with risk stratification; or (3) screening with body mass index or fasting plasma glucose. They found that one third of IADPSG-positive women were at low risk for adverse outcomes and could be managed less intensively. They concluded that implementing IADPSG recommendations will “substantially increase GDM diagnosis” and that risk stratification in IADPSG-positive women may be needed to reduce overtreatment.

Furthermore, there are medicolegal issues that would be created by the new diagnostic threshold. For example, it may result in an excessive rate of cesarean deliveries, because patients with an estimated fetal weight of 4000 g and GDM are currently offered an elective cesarean delivery, and such deliveries are associated with a number of maternal and fetal complications, including infection, excess bleeding, bowel problems, more neonatal intensive care admissions, and even death. Thus, if the
cesarean delivery rate increases due to a GDM diagnostic change, there may be significantly more maternal and fetal complications, which may offset the gains made by the increased diagnosis of this condition. There also is the economic issue of the medical expenditures, monitoring, and treatment expected from obstetricians when new diagnoses are made.

Cundy has further argued that, “the concentration on mild degrees of hyperglycaemia may well be misplaced, as most of the outcomes usually attributed to gestational diabetes are more strongly associated with maternal obesity and weight gain in pregnancy. The new testing procedure (with a GDM diagnosis based on a single plasma glucose measurement) will inevitably be imprecise. Given the many reservations about the new criteria, an urgent but dispassionate debate is required on the risks, costs, and benefits of their introduction.”

Summary and conclusions
GDM, which was once believed to be a relatively mild condition with few lasting consequences, is now known to bring significant short- and long-term adverse health effects for both women and their offspring. As the HAPO study and other follow-up investigations have demonstrated, even mild degrees of hyperglycaemia during pregnancy can have unwanted impacts on the mother’s and her baby’s health. Thus, some have called for adopting more sensitive diagnostic and screening methods to identify as many women with GDM as possible.

On the other hand, others are concerned that potentially tripling the number of patients diagnosed with GDM, without definitive evidence of a clear benefit for these women, will stress an already overburdened health care system. They are especially concerned that recommendations to change current GDM screening and diagnostic practices without specific recommendations and strategies for bolstering the primary care and obstetrics clinical support systems—and giving them the proper tools to mitigate risks—may be premature, and, thus, ultimately will not produce the desired benefits.

Although it is desirable from a public health standpoint to potentially prevent downstream consequences for women with milder forms of GDM and their babies, it also is prudent to be prepared to accommodate the onslaught of new patients such a change in current diagnostic and screening practices is liable to entail. More importantly, we also must be able to ensure that we know more precisely the level of care these women will require and whether the prescribed care will produce the improved outcomes we—and they—desire. Otherwise, we may find ourselves plunging headlong into a workforce shortage abyss from which it will be difficult to escape.

Indeed, the limited cost-benefit data available on the proposed changes suggest that the ability of increased GDM diagnosis to produce these anticipated benefits would depend on the universal availability and delivery of effective treatment, without an excess of treatment-associated risk. Neither of these assumptions is adequately supported by data. Although the anticipated benefits include decreased rates of downstream maternal and offspring obesity, metabolic syndrome, and diabetes, it is not yet clear how these benefits can be achieved in an environment of significantly restricted health care resources. In addition, if the proposed changes result in a dramatic increase in the rate of cesarean deliveries, the benefits of better diagnosis may be offset by increased cesarean delivery–related complications and costs.

It is highly possible that the answers to these and other key questions posed by deciding to change or not to change may not come from a single “meeting of the minds.” Rather, it may take a carefully laid out series of steps, each designed to answer key intermediate questions, leading to an ultimate set of answers. Either decision is not a benign one and needs to be made not only on the best available evidence, but also on the best evidence that we are capable of obtaining. Such questions can only be answered after a careful analysis of the currently available data, evidence-based comparisons of the various screening and diagnostic approaches currently in clinical use, and, quite possibly, additional, prospective research.

Thus, it is the hope of many in the field of diabetes and pregnancy that this NIH ODP–sponsored consensus conference will carefully and comprehensively examine both the pros and cons of all the issues involved in changing current GDM diagnostic and screening practices. These are complex questions with, undoubtedly, equally complex answers that could have enormous consequences in health care delivery globally. If appropriate data are unavailable to answer these questions, then the consensus conference participants must be willing to suggest to NIH and other federal funding agencies new research that can. In other words, if we can’t definitively answer, as Shakespeare would have put it, the question of whether ’tis nobler to change or not to change, now is the time to look very carefully before we leap!

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