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Q&A

Gestational Diabetes Mellitus: Why the Controversy?

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Gestational diabetes mellitus (GDM)[6] has been defined as "any degree of glucose intolerance with onset or first recognition during pregnancy." With the dramatic rise in the prevalence of type 2 diabetes, some organizations have advocated that hyperglycemia first detected in pregnancy should be classified as either diabetes mellitus in pregnancy or GDM. The rationale for identifying GDM is that it results in complications for both the fetus (e.g., large baby, neonatal hypoglycemia) and mother (e.g., preeclampsia, increased risk of cesarean delivery, and markedly increased likelihood of subsequent type 2 diabetes). Treatment of GDM reduces some of the adverse outcomes.

Despite the 5 international workshops devoted to GDM since 1979, there is considerable controversy surrounding identification of GDM. Both the screening and diagnostic criteria vary among countries and commonly between obstetric and diabetes organizations in a single country. Recommendations for screening encompass "do not screen," selective screening (high risk only), and universal. Moreover, the screening techniques vary; fasting glucose, random glucose, and oral glucose challenge are all used. The criteria for diagnosis are even more controversial. The major items of contention are the number of steps (1 or 2), the glucose load (75 g or 100 g), the duration of the test (2 h or 3 h), the glucose cutoff values, and whether 1 or 2 high glucose values are required.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was designed to determine the relationship between maternal blood glucose concentrations and adverse pregnancy outcomes. The prospective, randomized, multinational study included 23316 women who had a 75-g oral glucose tolerance test (OGTT) at 24–32 weeks of gestation. The study showed that the risk of adverse events increased continuously as a function of maternal glycemia. No convenient thresholds for increased risk were observed, and each of the 3 values (fasting, 1 h, and 2 h) independently contributed to adverse outcomes. On the basis of these data, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) suggested that a 75-g OGTT be performed and that GDM be diagnosed if any one of the following is equaled or exceeded: fasting plasma glucose (FPG) (92 mg/dL; 5.1 mmol/L), 1 h (180 mg/dL; 10 mmol/L), and 2 h (153 mg/dL; 8.5 mmol/L). The IADPSG guidelines are the first evidence-based, large-scale guidelines for GDM that relate maternal glycemia to outcomes. Unfortunately, the recommendations have failed to resolve the controversy and have not gained universal acceptance.

In this Q&A article, 4 international experts in perinatal medicine, endocrinology, and obstetrics and gynecology discuss the controversies surrounding GDM.

1. Should pregnant women be screened for GDM? If so, should screening be universal or performed only on those women at increased risk for GDM?

Tim Cundy: The answer to these questions, I believe, is complex and depends on many factors. We do know, though, that once the GDM label is applied, there are more interventions and more costs (of all sorts), so universal screening is likely to remain beyond the reach of most resource-poor countries.

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[6] Nonstandard abbreviations: GDM, gestational diabetes mellitus; HAPO, Hyperglycemia and Adverse Pregnancy Outcome; OGTT, oral glucose tolerance test; IADPSG, International Association of Diabetes and Pregnancy Study Groups; FPG, fasting plasma glucose; USPSTF, US Preventive Services Task Force; NDDG, National Diabetes Data Group; ACOG, American College of Obstetricians and Gynecologists; NICE, National Institute for Health and Care Excellence; RCT, randomized control trials; LGA, large-for-gestational-age; GCT, glucose challenge test; FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index; IDF, International Diabetes Federation; ADA, American Diabetes Association; ACHOIS, Australian Carbohydrate Intolerance Study in Pregnant Women; IVGTT, intravenous glucose tolerance test; PSG, pregnancy-specific glycoprotein; FABP, plasma fatty acid binding protein 4; RPB4, plasma retinol binding protein 4.

Donald Coustan: Testing for GDM should be universal, whether by a 2-step screening process or diagnostic testing. There is much confusion over the term "screening." Screening is usually defined as a test or procedure designed to detect asymptomatic individuals at a higher risk for a particular condition than the population at large. Those whose screening test is positive then undergo a diagnostic test. One type of screening is the 50-g glucose load, 1-h plasma glucose screen. Eliciting the presence of risk factors such as obesity or family history can also be considered a screening test. The real issue is whether blood testing should be universally applied. The answer to that question depends upon the prevalence of type 2 diabetes, and thus of GDM, in the population. In the United States, as in many parts of the world, there is an epidemic of type 2 diabetes that is, at least in part, related to the epidemic of overweight and obesity in our population. It is currently estimated that approximately 5% of women aged 18–44 have diabetes (half of whom are undiagnosed) and another 24% have prediabetes, meaning that almost one-third of women of reproductive age have suboptimal glucose metabolism. Depending upon the diagnostic criteria used, between 7% and >20% of pregnant women in the US have GDM. Given the prevalence of diabetes and prediabetes, this phenomenon should not be surprising. The various criteria currently used for diagnosing GDM are not dissimilar to the criteria for prediabetes, so these rates are consistent with each other. It has been shown that the use of historical risk factors to screen for GDM misses a large proportion of cases. So in a population with a high prevalence of diabetes, every pregnant woman should be tested for GDM.

Lois Donovan: Yes, pregnant women should be screened for GDM because identification of women with GDM allows treatment that has been shown consistently in randomized controlled trials and metaanalysis to improve pregnancy outcomes; specifically, reduced rates of shoulder dystocia, fetal overgrowth, and gestational hypertension.

A randomized control trial of universal vs risk factor-based screening for GDM found better pregnancy outcomes with universal screening. Universal screening has the additional benefit of ensuring that women who may lack risk factors for GDM and who have undiagnosed overt type 1 or 2 diabetes do not go undiagnosed in pregnancy. This is important because such women have a much greater risk of poor pregnancy outcomes than women with GDM. Therefore, I support universal screening for GDM but believe there is a role for more relaxed glycemic targets for the diagnosis of GDM when women lack additional risk factors for fetal overgrowth, gestational hypertension, and shoulder dystocia. GDM is not a disease. It is a marker of risk defined by agreed-upon cutoff values for acceptability of risk for outcomes (which follow a continuous curve without a distinct inflection point). Dysglycemia in pregnancy is just one of several risk factors for some negative pregnancy outcomes and for future development of maternal diabetes. False positive testing for GDM can have negative consequences because the label of "GDM" has been associated with practices that may not always be indicated.

Moshe Hod: Globally there are approximately 130 million births annually, 85% of which occur in low- and low–middle-income countries with limited resources; almost half of them in countries in east and south Asia who are at extremely high risk and would qualify for universal testing. Implementing universal testing on such a large scale is a truly Herculean task. Risk factors to help identify women who could be prioritized for testing have been described. Unfortunately, as shown in multiple studies, risk factor-based screening fails to identify a substantial proportion of women, supporting the contention that identification of women with hyperglycemia in pregnancy requires testing of all pregnant women. Another point supporting universal screening is that even in populations with supposedly lower risk, the age at conception is rising as more working women delay starting a family and rates of overweight, obesity, prediabetes, and diabetes (often undetected) are rising rapidly in reproductive-age women. Concerns are expressed, particularly from the developed world, that universal testing and (consequently) increased diagnosis would place additional logistical and economic challenges on healthcare systems. However, complex protocols for testing based on risk factors place high demands on healthcare providers and result in lower compliance and missed diagnoses. So, the answer is yes, all women must be tested. Instead of debating whether all women should be tested, we should try to develop

protocols to make the testing simple, user friendly, and effective.

2. What criteria should be used for screening and diagnosis of GDM?

Tim Cundy: Well, it should depend on what you are trying to achieve, and that has never been made explicit. In 1979, when GDM was declared "a major public health problem" (seemingly on no grounds whatsoever), the diagnostic criteria were based on the mother's future risk of type 2 diabetes. It was not until 2005–2009 that we saw randomized controlled trials of treatment of women at the milder end of the GDM spectrum and the HAPO study that explored the association between maternal blood glucose values and a selection of pregnancy outcomes. Until we can agree on what we are trying to prevent by screening and diagnosis and how successful treatment is, then it's going to be difficult to agree on criteria.

Donald Coustan: There are currently 2 competing approaches to the detection of GDM. The paradigm most commonly used in the US is a 2-step process. An initial 50-g glucose load, 1-h plasma glucose screening test is administered at 24–28 weeks gestation. If a predetermined threshold is met or exceeded, the second step is to administer a 100-g glucose load, 2-h OGTT (the diagnostic test). Thresholds of 130 mg/dL (7.2 mmol/L), 135 mg/dL (7.5 mmol/L), and 140 mg/dL (7.8 mmol/L) have been recommended for the initial 1-h screening test. The choice of a threshold for further testing requires a tradeoff between sensitivity and specificity. A lower threshold detects a higher proportion of cases, but it also requires the diagnostic test to be administered to a larger proportion of the population. A 2013 systematic review for the US Preventive Services Task Force (USPSTF) found that using a 130 mg/dL (7.2 mmol/L) threshold and the most commonly used diagnostic criteria (Carpenter & Coustan, see below) would identify 99% of GDMs (CI 95%–100%), but it would require diagnostic testing in approximately 23% of the normal population (CI 17%–32%). A 140 mg/dL (7.8 mmol/L) threshold would identify only 85% of GDMs (CI 76%–90%), but it would require diagnostic testing in only 14% of normal individuals (CI 10%–20%). In our center, we use the 130 mg/dL (7.2 mmol/L) threshold, reasoning that diagnosing GDM is a worthwhile opportunity to prevent adverse outcomes in the pregnancy, as well as to intervene to prevent type 2 diabetes in the mother.

There are 2 sets of diagnostic criteria recommended for the 2-step process in the US; both are based on the "O'Sullivan criteria" for the 100-g glucose load, 3-h OGTT derived by using 2 standard deviations above the mean for each of the 4 glucose values. Because venous whole blood glucose samples were used in the original criteria, the National Diabetes Data Group (NDDG) published conversions to plasma samples, adding 15% to each of the cutoff values, in 1979. At around the same time, Marshall Carpenter and I calculated and published conversions based on both the use of more specific enzymatic methods for glucose measurement (5 mg/dL; 0.3 mmol/L decrease) and plasma samples (14% increase). These are the "Carpenter & Coustan" (C&C) criteria. The original O'Sullivan criteria were validated based upon their predictive value for future type 2 diabetes in the mothers, with approximately 50% developing diabetes within 20 years of their index pregnancy. While either set of converted criteria is considered acceptable by the American College of Obstetricians and Gynecologists (ACOG), a subsequent head-to-head comparison in which the same samples were run using the old (whole blood, Somogyi–Nelson) and current (plasma, glucose oxidase) methodologies found that only the C&C criteria were within 95% confidence intervals of the original O'Sullivan criteria. Therefore, I believe that if the 2-step process with the 100-g glucose load, 3-h OGTT is to be used, then the C&C criteria are most appropriate.

In 2010, the IADPSG published recommendations for a 1-step approach to the diagnosis of GDM. No screening test was recommended; rather, a diagnostic 2-h 75-g OGTT would be administered to all pregnant women at 24–28 weeks unless they have already been diagnosed with diabetes. According to the IADPSG, the thresholds for the diagnosis of GDM were based on, among other things, an analysis of the data from the HAPO study, and they were chosen to identify patients whose odds ratios for adverse outcomes such as macrosomia, neonatal increased body fat, and fetal hyperinsulinemia were >1.75 compared to patients with median glucose values. A single increased glucose value identifies GDM, and patients so identified have approximately twice the likelihood of adverse pregnancy outcomes compared to patients without GDM. Unlike the criteria for the 100-g, 3-h OGTT, these criteria are based on pregnancy outcomes, which are the primary reason for diagnosing GDM. Although identifying people at risk for future diabetes is a worthwhile endeavor, it should not be confined to pregnant women because women who never have children and men can also develop diabetes. The main reason we seek to diagnose GDM is prevention of adverse pregnancy outcomes, so it would make sense to use criteria based on the risk of such adverse outcomes. The IADPSG criteria are being used increasingly throughout the world.

Another recommendation of the IADPSG was to test for preexisting diabetes at the first prenatal visit in women at high risk for diabetes or in all gravidas. The diagnostic criteria are the same as in nonpregnant individuals. Some confusion arose because the recommendation was that if fasting plasma glucose was above the

IADPSG cutoff value for GDM (92 mg/dL; 5.1 mmol/L) but below the cutoff value for type 2 diabetes (126 mg/dL; 7.0 mmol/L), the patient could be diagnosed with GDM. It was subsequently clarified that the IADPSG diagnostic criteria for GDM were derived from 75-g, 2-hr OGTTs performed after 24 weeks gestation, and the data were not necessarily applicable in the first or early second trimester. If the diagnosis of GDM is made in early pregnancy, there is little evidence that intervention at such an early time provides meaningful benefit to the patient. The reason for early testing is to uncover preexisting diabetes that was previously undiagnosed because interventions such as prenatal diagnosis of congenital malformations and intensive control of hyperglycemia are of significant benefit. The standard diagnostic tests for diabetes in nonpregnant individuals include hemoglobin A1c (HbA1c), fasting plasma glucose or the 75-g, 2-hr OGTT. I prefer the HbA1c test administered at the first prenatal visit because it is convenient and does not require any preparation such as fasting. If the result is diagnostic of diabetes (i.e., ≥6.5%), the patient is assumed to have preexisting diabetes. Uncertainty arises when the result is compatible with prediabetes (5.7%–6.4%). Such a result is not diagnostic of GDM. A recent pilot study suggested that such patients have an approximately 25% chance of having GDM when tested at 24–28 weeks.

It should be mentioned that although the 2 approaches described above are most commonly in use around the world, other approaches exist, such as the National Institute for Health and Care Excellence (NICE) guidelines that are used in parts of the UK. It is beyond the scope of this response to describe them all. My recommendation is to test with HbA1c at the first prenatal visit, and then, at 24–28 weeks, to use either the 1-step or 2-step approach depending upon the protocol in place in the community. It is my hope and expectation that the 1-step approach as recommended by IADPSG will eventually be adopted universally.

Lois Donovan: The 50-g glucose challenge is an easily implemented and widely accepted method of screening for GDM. It has been shown to substantially reduce the need for the more resource-intensive fasting 75-g OGTT. No screening test is perfect. A systematic review suggests use of the 50-g glucose load screen at a threshold of 140 mg/dL (7.8 mmol/L) in a cohort of 1000 women misses 10 cases of GDM that would have been diagnosed by OGTT. This, however, may not be a serious limitation because women with a negative 50-g glucose screen have low rates of GDM-related outcomes. Furthermore, a 2-step approach to GDM diagnosis and screening has been found to be cost effective. To my knowledge, the 50-g glucose challenge has not been validated for diagnosis by the IADPSG criteria; however, a number of studies have reported the prevalence of GDM and pregnancy outcomes for women with a positive 50-g glucose screen in women who met IADPSG glucose thresholds.

I believe that the 75-g OGTT is strongly preferred to the 3-h 100-g OGTT as a diagnostic test for GDM because it is more convenient and less costly to implement. The HAPO study and its predecessor confirmed a continuous positive relationship, with no clear inflection point, between increasing glucose values on the 75-g OGTT and adverse pregnancy outcomes that have been shown to be modifiable by management of GDM.

The lack of randomized control trials (RCTs) comparing the impact of treatment on women who meet different glucose criteria means that the diagnostic thresholds for GDM will remain arbitrary and influenced by the health priorities and cost of implementation in the setting in which they are used.

I favor greater consideration of maternal body mass index (BMI) in the determination of glycemic thresholds for diagnosis of GDM. The HAPO study showed that maternal BMI had a greater impact on the odds of having a large-for-gestational-age (LGA) infant than glucose values below fasting of 100 mg/dL (5.6 mmol/L), 1 h of 212 mg/dL (11.8 mmol/L), and 2 h of 178 mg/dL (9.9 mmol/L). A reanalysis of a randomized control trial in women with mild GDM failed to demonstrate the beneficial effects of GDM therapy for fetal overgrowth in normal-weight women. Thus, differing diagnostic thresholds on a 75-g OGTT could be used based on maternal BMI. For example, the glucose thresholds on a 75-g OGTT from the HAPO study that corresponds to a 2.25-fold increased risk of LGA could be used for normal-weight women. The glucose thresholds that correspond to a 2-fold increased risk of LGA [i.e., 95 mg/dL (5.3 mmol/L) fasting, 190 mg/dL (10.6 mmol/L) at 1 h, and 162 mg/dL (9.0 mmol/L) at 2 h] could be used for women who are overweight (BMI 25–29.9) and the IADPSG glucose thresholds that correspond to a 1.75-fold increased risk of LGA predominately could be used for women who are obese (BMI >30). Further research is required to validate such an approach.

Moshe Hod: The association between maternal plasma glucose concentrations and adverse pregnancy outcomes is linear and continuous, with no infliction point, making it difficult to define clear diagnostic thresholds. Also, the association is relevant both in relation to fasting and postglucose challenge values. Some countries and professional organizations, although accepting universal testing, recommend a 2-step approach: a 50-g nonfasting glucose challenge test (GCT), followed by a 75-g OGTT in women who test positive upon initial screening. Although this reduces the number of OGTTs and in the view of its proponents "ensures that women diagnosed with GDM have significant glucose intolerance," it fails

to take into account the fact that GCT will not identify all women manifesting only fasting hyperglycemia as they will not qualify for the subsequent OGTT and will also miss around 25% of cases with OGTT abnormalities. Moreover, a significant proportion of women with positive GCT fail to complete the evaluation as they do not turn up for the OGTT. This approach therefore misses many women with hyperglycemia in pregnancy. Therefore, the International Federation of Gynecology and Obstetrics (FIGO), WHO, and the IADPSG guidelines recommend universal testing using a single-step 75-g OGTT.

Although it would be preferable to have uniform global diagnostic cutoff values, in view of the continuous linear association between maternal glycaemia and perinatal outcomes, any set of diagnostic criteria proposed will need to evolve from a consensus approach, balancing risks and benefits in particular social, economic, and clinical contexts. Mean glucose values for fasting, 1-h, and 2-h 75-g OGTTs based on an acceptable odds ratio of 1.75 for markers of diabetic fetopathy (LGA, excess fetal adiposity, and fetal hyperinsulinemia) in the HAPO study were proposed as diagnostic cutoff values by IADPSG. These cutoff values were accepted and endorsed by the WHO and now also by FIGO.

3. Essentially all influential clinical diabetes organizations endorse the same diagnostic criteria for diabetes in nonpregnant individuals. Why do the screening and diagnostic criteria for GDM differ among countries and frequently between obstetric and diabetes organizations in a single country?

Tim Cundy: The diagnostic criteria in nonpregnant people are based on the glucose concentrations at which microvascular complications (in particular, retinopathy) start to appear. Everyone agrees about this. For GDM, there is little agreement on what outcomes are important and no evidence that adopting particular criteria improves those outcomes. The criteria suggested in 2010 by the HAPO-based IADPSG increased hugely the proportion of pregnancies that are labeled as having "GDM" (to 1 in 5 pregnancies in the USA and nearly 1 in 2 in Southern China), but there is no evidence from RCT to show the benefit of treatment using this approach. In 2013, the WHO in a lukewarm endorsement of the IADPSG criteria described the quality of evidence for its recommendation as "very low" and the strength of its recommendation as "weak." Anyone with a critical eye and a concern for costs and overdiagnosis should be skeptical, hence the differences in opinion.

Donald Coustan: One of the main motivators for the HAPO study was the presence of multiple diagnostic criteria for GDM around the world. Glucose loads in use included 50, 75, and 100 g. Different cutoff values were recommended in various countries. It was impossible to compare data from one place to another. The HAPO study included pregnant women from 15 field centers in 9 different countries to assure relevance to all populations. The subsequent IADPSG recommendations were intended to bring uniformity to diagnosing GDM, as is the case with criteria for diabetes in nonpregnant individuals. Because of reliance on a single increased OGTT value rather than insistence upon at least 2 increased values, the IADPSG criteria increase the rate of GDM by a factor of 2–3. The IADPSG criteria have now been adopted by numerous national and international organizations, including the WHO, the International Diabetes Federation (IDF), FIGO, and the American Diabetes Association (ADA), which allows that either approach is acceptable. A 2013 NIH-sponsored consensus development conference recommended the 2-step approach, noting that the increased GDM rate related to the IADPSG recommendation for a 1-step approach would increase healthcare costs, and the benefits of using the new criteria were unproven. This point of view was echoed by the ACOG recommendation of continuing the 2-step approach. Although it is true that there has been no RCT of diagnosing and treating GDM based on the IADPSG criteria, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) RCT demonstrated benefit using even lower diagnostic criteria (2-h value of 140–199 mg/dL; 7.8–11.1 mmol/L rather than the IADPSG threshold of 153 mg/dL; 8.5 mmol/L). Furthermore, the approximately 18% GDM rate with the new criteria parallels the global increase in type 2 diabetes. I believe that we are in a process of transition, and that as more experience with the IADPSG recommendations leads to the accumulation of more data, the 1-step process will become more universally adopted.

Lois Donovan: The glucose criteria for diagnosing diabetes in nonpregnant individuals, although similar among diabetes organizations, has also changed over the years and continues to evolve. The prevalence of retinopathy at the previous fasting glucose criterion for a diagnosis of diabetes [i.e., 140 mg/dL (7.8 mmol/L)] was found to be much higher than at the postglucose load thresholds for diagnosing diabetes of 200 mg/dL (11.1 mmol/L). This resulted in lowering of the fasting glucose threshold for a diagnosis of diabetes to 126 mg/dL (7.0 mmol/L) to reflect a similar level of risk of retinopathy for the fasting glucose threshold. The HAPO study results provided an opportunity to ensure that the fasting, 1-h, and 2-h postglucose load thresholds for diagnosing GDM are of similar risk for pregnancy outcomes of concern. Diagnostic criteria for GDM continue to differ among countries and obstetric and diabetes organizations in a single country because there is no clear inflection

point for risk of pregnancy outcomes with increasing glucose. This leaves open the determination of what level of risk is "acceptable." Organizations differ in the level of concern they have for a plethora of different pregnancy outcomes examined in the HAPO study. Some organizations are more comfortable with greater risk for certain outcomes that are of less concern to them.

Moshe Hod: Diagnostic criteria for diabetes in nonpregnant individuals are based on analysis of large-scale data on the association between plasma glucose values and the future risk of diabetes complications. While the association is continuous here too, there is nonetheless a clear threshold where specifically glycemia-associated complications—namely, microvascular—exhibit a sharp increase, making it easier to define diagnostic values. In contrast, the immediate perinatal outcomes in hyperglycemic pregnancies do not have a clear threshold. Also, while maternal glucose concentration is an important contributor to LGA and fetal adiposity, which are important markers for perinatal complications, they are not solely dependent on maternal glucose. For example, in using a 2-h glucose cutoff value of 8.5 mmol/L or 153 mg/dL based on an odds ratio of 1.75 for adverse outcomes derived from HAPO data as per the IADPSG recommendation may not be as efficient in identifying women at risk for fetal overgrowth as those identified by having a 2-h glucose corresponding to a slightly lower odds ratio, e.g., 1.5. The latter corresponds to the older WHO criteria 2-h value of 7.8 mmol/L or 140 mg/dL. This may be of importance in developing countries, particularly in South Asia, where women are relatively small and a larger baby may pose greater obstetric risk. A lower postload glucose threshold to diagnose GDM in South Asian women may therefore be considered appropriate. GDM diagnostic thresholds that are linked to perinatal outcomes, as they should rightly be, unlike previous criteria that were linked to future risk of diabetes in the mother, must take into account how the risk of a large fetus plays out in the context of maternal size.

Fasting glucose values decline between early pregnancy and mid-trimester, and thus using the same cutoff value to diagnose GDM in early pregnancy and at 24–28 weeks may be inappropriate, as shown in large studies from China. Also, Asian women tend to have lower fasting glucose values, and thus a fasting cutoff value of 92 mg/dL (5.1 mmol/L) as per the IADPSG and WHO 2013 criteria may be too high to be the sole criterion to pick up GDM cases, as seen in women from Asian centers in the HAPO study and a study on Asian women in the UK.

There is also an argument that if the accepted treatment target for fasting glucose is <95 mg/dL (5.3 mmol/L), that for 1-h postprandial is <140 mg/dL (7.8 mmol/L), and that the 2-h postprandial treatment target to obtain best perinatal outcome is <120 mg/dL (6.7 mmol/L), then why should the diagnostic criteria for the fasting value be set lower and that for 1 h and 2 h be set much higher?

The variability in diagnostic cutoff values between countries and medical specialties is therefore a reflection of the variable perspectives. Although it would be preferable to have uniform global diagnostic cutoff values, in view of the continuous linear association between maternal glycemia and perinatal outcomes, any set of diagnostic criteria proposed will need to evolve from a consensus approach, balancing risks and benefits in particular social, economic, and clinical contexts. FIGO has taken cognizance of these issues in its recommendations and guidelines.

4. Has the HAPO study had a substantial influence on clinical practice?

Tim Cundy: Yes, but maybe not in the way it should have. HAPO confirmed earlier data that there was a linear relationship between maternal blood glucose values and birth weight. The incidence of clinical neonatal hypoglycemia was low across the range of blood glucose values (<3%) except when the fasting glucose was ≥100 mg/dL (5.6 mmol/L). The associations of birth weight and cesarean section rate with blood glucose were markedly confounded by maternal adiposity. It would have been good for the IADPSG to pause at this point and think about what we are trying to achieve, whether it can be achieved, and how significant a factor mild GDM really is before rushing to develop new diagnostic criteria.

Donald Coustan: The HAPO study has improved our understanding of the basic biological relationship between fetal glucose exposure (as early as 24–28 weeks) and fetal insulin production with subsequent fetal growth and overgrowth, neonatal fat accretion, and various adverse pregnancy outcomes. Ongoing follow-up studies will determine whether the effects of intrauterine exposure to increasing glucose concentrations will carry over into childhood and beyond. The IADPSG recommendations, primarily based upon the HAPO study findings, have had a substantial impact on clinical care in many parts of the world, although in the US most obstetric caregivers have not yet adopted the new criteria.

Lois Donovan: The HAPO study has been used to derive glucose thresholds of equivalent risk for pregnancy outcomes of interest for the fasting, 1-h, and 2-h results on a 75-g OGTT. This has resulted in the derivation of some different glucose thresholds for the diagnosis of GDM that are now used in clinical practice, including the IADPSG criteria and the Canadian Diabetes Association preferred criteria.

Moshe Hod: While it is difficult to judge how much the HAPO study has influenced clinical practice, one thing is certain, that it did "let the cat among the pigeons" and stimulated debate and discussion, which over time has brought highly influential and important organizations (but hitherto relatively passive on the subject) such as FIGO to the center stage. This has attracted the attention of obstetricians around the world, particularly in countries with the highest burden, and stirred action. So yes, in a way, the HAPO study acted as a catalyst for change, but unfortunately not in the countries and regions where the main study centers were located, where there has been no change in policy.

5. Could approaches other than an oral glucose load, which is unpalatable to many pregnant women, be used for identifying GDM in the foreseeable future?

Tim Cundy: One of the problems with the definition of GDM [". . . any degree of glucose intolerance of onset or first detected in pregnancy irrespective of whether the condition persists after pregnancy (and) does not exclude the possibility that (it) antedated pregnancy"] is that it conflates trivial increases in maternal glucose with full blown but previously unrecognized, diabetes (usually type 2) and implies that the risks are the same across this spectrum. Clearly, they are not. Serious adverse outcomes (including congenital anomalies and stillbirth) are real risks for women with unrecognized diabetes. Type 2 diabetes first detected in pregnancy is not uncommon, particularly in communities where obesity is prevalent. Early pregnancy screening with a fasting blood glucose or HbA1c would seem the logical way to detect such cases.

Donald Coustan: Many alternative approaches have been tried, including mixed meals, candy bars, or jelly beans. None is as well characterized as the OGTT. While the ingestion of substances other than glucose may evoke quantitatively and qualitatively different metabolic responses, such substitutes may be useful when patients cannot tolerate the pure glucose load. The use of a 75-g challenge rather than the traditional 100-g challenge may make the test more palatable. I have found that serving the glucose load on crushed ice makes it considerably less noxious to many women. One difficult situation becoming increasingly common is the patient who has undergone gastric bypass. Many simply cannot tolerate the osmotic load of a pure glucose challenge. In these circumstances, we use an intravenous glucose tolerance test (IVGTT) by injecting 25 g of glucose over 2–4 min, with calculation of a k_t value, the glucose disappearance rate, based upon the ratio of a 10-min plasma glucose to a 60-min plasma glucose. The only pregnancy data I have found were published in 1982, so their relevance is questionable. It is also of concern that even patients who have undergone gastric bypass take in their nourishment orally, whereas the IVGTT bypasses enterohepatic absorption and thus may not be as reflective of day-to-day life. Nevertheless, it is a reasonable compromise for some patients.

Lois Donovan: For women who do not tolerate an oral glucose load, fasting glucose at a threshold of 85 mg/dL (4.7 mmol/L) at or after 24 weeks gestation is an attractive alternative screen with similar sensitivity to the 50-g oral glucose challenge test (87%) for predicting OGTT results. Although the specificity (52%) of fasting glucose for predicting the OGTT results is poorer than that of the 50-g glucose challenge test (69%–89%), fasting plasma glucose is more reproducible than postglucose load testing and has been directly related to pregnancy outcomes. Therefore, a fasting plasma glucose of <85 mg/dL (4.7 mmol/L) is good at identifying women who do not have GDM. However, the 50-g glucose challenge test is better at identifying women who have GDM. If the fasting plasma glucose result at or after 24 weeks gestation is above the fasting glucose threshold used for a diagnosis of GDM, then GDM can be assumed. If the fasting plasma glucose after 24 weeks gestation is less than the diagnostic for GDM but at or above 85 mg/dL (4.7 mmol/L), further testing is required; assuming these women could not tolerate an oral glucose load, then laboratory or capillary glucose testing following meals and/or assessment of fetal size is required to clarify management needs. HbA1c is too insensitive for diagnosing GDM.

Moshe Hod: One of the reasons that testing for GDM is so difficult is because of the challenge with regard to the OGTT. Many women cannot tolerate the oral glucose load, requiring them to come back for testing. Similarly, in many settings in developing countries, women do not attend antenatal clinics in the fasting state and when asked to come back, they will just drop out. Many women living in rural remote areas with poor transport facilities find it difficult to remain fasting as they have to travel long distances to get to the testing center and wait for their turn because of the heavy patient load. Thus, both fasting and oral glucose load create logistical problems. Other tests for the diagnosis of diabetes, such as HbA1c, while useful for diagnosing diabetes during pregnancy, are not reliable for diagnosing gestational hyperglycemia. Glycated albumin has been considered but at present there are limited data to recommend its use. Other glycated proteins such as glycated fibronectin and glycated pregnancy-specific glycoprotein (PSG), glycated complement regulatory protein CD59, plasma fatty acid binding protein 4 (FABP4), plasma retinol binding protein 4 (RBP4), and plasma adipocytokine are being investigated for their potential to diagnose GDM without

the need for fasting and oral glucose administration. While they have shown promise in early studies, it will take several years and large-scale studies to prove their claims. If they do prove to be useful, the next issue will be how expensive these tests will be compared to the 75-g OGTT.

6. What is needed for international consensus for screening and diagnosis of GDM? Will it ever be achieved?

Tim Cundy: Since 2010, papers about GDM are published, on average, every 9 h. With such an outpouring of information, how come we can't agree on anything? Rather than conclude that the answers are within reach if only we had more research, maybe we should think more about what the questions are. What are we trying to achieve?

The RCTs demonstrated that treatment for mild GDM on average lowered birth weight by approximately 100 g and reduced the already low rates of shoulder dystocia and preeclampsia (though it's not clear to what extent these gains were due to the mothers having lower glucose concentrations or less gestational weight gain). So, is the main aim to prevent babies getting too large? Is mild GDM the only culprit here? Maternal obesity and excessive gestational weight gain are arguably more important in accelerating fetal growth. Are we really doing any good lowering mildly increased blood glucose in women whose babies are already growing slowly?

It is often argued that detecting and treating GDM will help prevent the development of type 2 diabetes in the mothers and obesity in the offspring. Although it would be nice if true, none of the follow-up studies lends any credence to these claims.

I am aware of the cries for "consensus" on screening and diagnosis, but would agreeing to an evidence-free consensus really be an advance? Let's address and answer some of these other questions first.

Donald Coustan: Change is a process, and does not happen all at once. It takes time.

Lois Donovan: RCTs comparing the impact of treatment on pregnant women who meet various different BMI and glucose criteria are required if we are going to reach a consensus on screening and diagnosis of GDM. If long-term benefit to the offspring of woman randomized to treatment of GDM is ever shown, this would greatly influence international consensus for GDM screening and diagnosis.

Moshe Hod: There are a few points on which consensus can be reached quite easily because of the available evidence.

The first is that risk-based testing should be abandoned and all women should be offered testing for hyperglycemia during pregnancy. Also, testing should be done as soon as possible after presentation to rule out previously unknown diabetes and repeated at 24–28 weeks. In women with risk factors, testing should be more aggressive, i.e., testing in each trimester.

The second is that testing should be a 1-step procedure because the 2-step procedure with an initial 50-g nonfasting glucose challenge test followed by 50-g OGTT filters out a lot of women who are at risk of complications. These women, if identified, can benefit from simple low-cost nonpharmacological interventions and can be offered the possibility of primary prevention of diabetes postpregnancy through health promotion.

It may be a little more difficult to achieve international consensus on diagnostic thresholds and the most appropriate tests to use, such as fasting, 75-g OGTT, etc., in different resource settings. This is also the position of FIGO in its pragmatic recommendations.

Perhaps development of an easy-to-use point-of-care nonfasting, nonglucose load-dependent test may make consensus easier to achieve in the future.

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