Diagnosis of Gestational Diabetes Mellitus: It Is Time for International Consensus

David B. Sacks*

Gestational diabetes mellitus (GDM)\(^1\) has been defined as any degree of glucose intolerance with an onset or first recognition during pregnancy (1–3). Fetal complications of GDM include macrosomia (large baby, which leads to birth injuries), shoulder dystocia, and neonatal hypoglycemia, and adverse outcomes for the mother are an increased risk of cesarean delivery, pre-eclampsia, and hypertension during pregnancy, as well as a significantly higher risk of subsequent type 2 diabetes. Treating women with GDM reduces at least some of the adverse outcomes (4). Estimates of the prevalence of GDM range from <1% to 28%, reflecting the different diagnostic criteria and populations studied. The increasing prevalence of GDM in the US is congruent with the marked increase in obesity and type 2 diabetes.

Pregnant women have been evaluated for diabetes for more than 50 years. Notwithstanding the 5 international workshops devoted to GDM that have been held between 1979 and 2005, there is lack of agreement concerning the optimal method to identify “any degree of glucose intolerance.” The criteria for both screening and diagnosing GDM vary considerably among countries and often between diabetes and obstetric organizations in a single country (5). Screening recommendations range from none (do not screen) to selective (screen only those at high risk) to universal. Approaches for screening tests include fasting glucose, random glucose, or, more commonly, a glucose challenge in which the patient ingests 50 g glucose (regardless of the time of the last meal). If the 1-h postload plasma glucose concentration exceeds the threshold, a full diagnostic oral glucose tolerance test (OGTT) is performed; however, 2 thresholds [140 mg/dL (7.8 mmol/L) or 130 mg/dL (7.2 mmol/L)] are generally used. Approximately 15% of women have concentrations that exceed the higher cutoff, which identifies approximately 80% of women with GDM, whereas the use of the lower cutoff increases the sensitivity to 90% but includes approximately 25% of pregnant women.

Diagnosis is made with an OGTT, but, again, the criteria vary. The O’Sullivan and Mahan criteria (Table 1) form the basis for the majority of diagnostic approaches. Proposed in 1964, these criteria were derived from 752 unselected, asymptomatic pregnant women who underwent a 3-h OGTT (6). GDM was defined as 2 or more values >2 SDs above the mean. Although these arbitrary criteria were established to predict the subsequent (postpartum) development of diabetes (not necessarily to identify pregnancies with an unfavorable outcome), they became widely adopted to diagnose GDM. The cutoffs have been modified to compensate for changes in glucose measurement. In the O’Sullivan and Mahan study, glucose was measured in whole blood with the Somogyi–Nelson method. The National Diabetes Data Group (NDDG) (7) advised in 1979 that plasma be the preferred sample for glucose analysis. The NDDG raised the cutoffs for GDM (Table 1), because glucose concentrations in plasma are approximately 11% higher than in whole blood (owing to the higher concentration of water in plasma). Another concern is that the Somogyi–Nelson method, which quantifies glucose according to its ability to reduce copper, is not specific for glucose. Therefore, Carpenter and Coustan (8) lowered the cutoffs (Table 1) to reflect the more specific enzymatic assays that replaced the colorimetric assays clinical laboratories had previously used. To convert the O’Sullivan and Mahan values, Carpenter and Coustan used the formula: Plasma glucose concentration = (whole-blood glucose concentration – 5 mg/dL) \times 1.14. In contrast to the 2-step procedures outlined above, the WHO recommends that GDM be diagnosed via a 1-step procedure that uses the same OGTT performed to diagnose diabetes in nonpregnant individuals, i.e., 75 g of glucose, with only the fasting and 2-h samples analyzed (Table 1). Thus, although the OGTT is universally used for diagnosis, there is no accord. The main issues in dispute are a glucose load of 100 g vs. 75 g, a duration of 2 h vs. 3 h, the cutoffs, and whether 1 or 2 high values are necessary.

A notable flaw in the GDM diagnostic criteria is that they have been based on the risk of future hyper-
glycemia, not on clinical sequelae. To address this deficiency the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was undertaken. The objective of this study was to determine the relationship between maternal blood glucose concentrations and adverse pregnancy outcomes. This prospective randomized multinational study included 23,316 women who underwent a 1-step, 75-g OGTT at 24 to 32 weeks of gestation (9).

Primary outcomes were a birth weight ≥90th percentile (macrosomia), primary cesarean section delivery, clinical neonatal hypoglycemia, and a cord C-peptide concentration ≥90th percentile (fetal hyperinsulinemia). The findings revealed that the risk of adverse maternal, fetal, and neonatal events increased continuously as a function of maternal glycemia, even within intervals that were previously considered normal for pregnancy (9). Similar associations were observed between glycemia and secondary outcomes of the study (preterm birth, shoulder dystocia, preeclampsia, and intensive neonatal care) (9). There were no thresholds at which risk increased (i.e., no convenient cutoffs), and each of the 3 values in the OGTT had an independent contribution to adverse outcome.

To translate the HAPO results into clinical practice, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) sponsored a workshop to develop recommendations for the diagnosis and classification of hyperglycemia in pregnancy (10).

On the basis of the HAPO data, the panel suggested that a 75-g OGTT be performed and that GDM be diagnosed if any one of the values for fasting plasma glucose, 1-h glucose, or 2-h glucose equaled or exceeded the diagnostic threshold in Table 1. Although the HAPO thresholds differ minimally from those of Carpenter and Coustan (Table 1), the prevalence of GDM in the US would increase from approximately 7% to 18% (i.e., from approximately 250,000 to 640,000 women per year). Similar increases are anticipated for other countries. The higher prevalence is due mainly to the HAPO requirement that only one of the OGTT values exceed the threshold (compared with 2 for most other organizations). The IADPSG panel advised that venous plasma or serum glucose be measured with an enzymatic method of high accuracy and low imprecision. Glycolysis was minimized in the HAPO study by collecting blood samples into tubes containing sodium fluoride, keeping the samples on ice until plasma was separated (1 h), and then freezing the plasma. All glucose concentrations were measured at a single central laboratory via a glucose oxidase method. Although these meticulous sample-handling procedures increase the confidence in the glucose concentrations measured in the study, they pose problems for glucose analysis in the context of routine patient care.

The IADPSG recommendations are the first large-scale evidence-based guidelines for GDM that correlate maternal glucose concentrations to outcomes. Nevertheless, they have been mired in controversy since their publication. Despite the diverse composition and broad representation of the members of the IADPSG panel (10), the recommendations have not gained universal acceptance. Although they have been adopted in several countries, including Canada, Germany, Italy, Japan, China, and Australia, the American Diabetes Association is the only influential clinical organization in the US to have endorsed them. The National Academy of Clinical Biochemistry has also endorsed the recommendations (3).

The American College of Obstetricians and Gynecologists recommends that GDM be diagnosed with either the NDDG or the Carpenter and Coustan (C&C) criteria. O’Sullivan, O’Sullivan and Mahan; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes. The ADA criteria were changed in 2011 to the IADPSG criteria.

### Table 1. Criteria for diagnosing GDM.

<table>
<thead>
<tr>
<th>Criteria&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Approach</th>
<th>No. of increased values</th>
<th>Year proposed</th>
<th>Glucose load, g</th>
<th>Glucose threshold, mg/dL (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting 1 h 2 h 3 h</td>
<td></td>
</tr>
<tr>
<td>O’Sullivan</td>
<td>2 step</td>
<td>2</td>
<td>1964</td>
<td>100</td>
<td>90 (5.0) 165 (9.2) 145 (8.1) 125 (6.9)</td>
</tr>
<tr>
<td>NDDG</td>
<td>2 step</td>
<td>2</td>
<td>1979</td>
<td>100</td>
<td>105 (5.8) 190 (10.6) 165 (9.2) 145 (8.1)</td>
</tr>
<tr>
<td>C&amp;C</td>
<td>2 step</td>
<td>2</td>
<td>1982</td>
<td>100</td>
<td>95 (5.3) 180 (10.0) 155 (8.6) 140 (7.8)</td>
</tr>
<tr>
<td>ADA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 step</td>
<td>2</td>
<td>2000</td>
<td>100</td>
<td>95 (5.3) 180 (10.0) 155 (8.6) 140 (7.8)</td>
</tr>
<tr>
<td>ADA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 step</td>
<td>2</td>
<td>2000</td>
<td>75</td>
<td>95 (5.3) 180 (10.0) 155 (8.6) 140 (7.8)</td>
</tr>
<tr>
<td>EASD</td>
<td>1 step</td>
<td>1</td>
<td>1996</td>
<td>75</td>
<td>108 (6.0) — 162 (9.0) —</td>
</tr>
<tr>
<td>WHO</td>
<td>1 step</td>
<td>1</td>
<td>1999</td>
<td>75</td>
<td>126 (7.0) — 140 (7.8) —</td>
</tr>
<tr>
<td>IADPSG</td>
<td>1 step</td>
<td>1</td>
<td>2010</td>
<td>75</td>
<td>92 (5.1) 180 (10.0) 153 (8.5) —</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adapted from Vandorsten et al. (11). The American College of Obstetricians and Gynecologists accepts either the NDDG or Carpenter and Coustan (C&C) criteria. O’Sullivan, O’Sullivan and Mahan; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes. The ADA criteria were changed in 2011 to the IADPSG criteria.
Coustan criteria. An NIH Consensus Development Conference was held in March 2013 to assess the available data regarding GDM diagnosis (11). The 15-member panel included representatives from the fields of obstetrics, pediatrics, maternal–fetal medicine, women’s health, diabetes, and epidemiology. After considerable deliberation, the panel concluded that although international standardization has benefits, the evidence is insufficient to adopt the IADPSG recommendations. The panel supported the continuation of the 2-step approach, which is largely confined to the US. The main reasons professed for not switching to the IADPSG criteria are the lack of evidence that the additional women identified will have improved outcomes (the HAPO study was observational) and the considerable cost to society incurred by the large increase in the number of individuals diagnosed with GDM.

The criteria for diagnosing diabetes in nonpregnant individuals have evolved over time, and essentially all major influential clinical diabetes organizations worldwide have accepted them. By contrast, several different schemes are used to diagnose GDM. The current situation for GDM is reminiscent of the wide variation in the diagnostic criteria used for nonpregnant individuals in the 1960s and the early 1970s (12), before the NDDG recommendations (7). The heterogeneity in the diagnostic criteria for GDM make it difficult to optimally manage the condition, accurately determine prevalence, establish risk of progression to diabetes postpartum, evaluate possible variations among ethnic groups, and compare published studies. Importantly, GDM has adverse outcomes for both mother and baby, and these effects can be mitigated by recognition and treatment (13, 14). There is an urgent need for universal guidelines. A rational approach to define cutoffs for diagnosis should be based on the correlation of blood glucose concentrations and the risk of subsequent complications. That would enable clinicians to reduce the morbidity and mortality associated with GDM.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

Employment or Leadership: D.B. Sacks, Clinical Chemistry, AACC.

Consultant or Advisory Role: None declared.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: D.B. Sacks, Intramural Research Program of the NIH.

Expert Testimony: None declared.

Patents: None declared.

References


