Various challenge tests have been used around the world for the diagnosis of gestational diabetes mellitus (GDM), and substantial variation among these methods has been noted, not only in the amount of glucose for the challenge and the testing intervals but also in the concentration thresholds used for interpretation. The interpretive criteria for these testing approaches have variably been based on the value for predicting future maternal diabetes or been adopted from standards developed with nonpregnant individuals, despite the changes in glucose metabolism known to occur during pregnancy. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study was an observational study of values obtained in blinded 75-g, 2-h oral glucose tolerance tests (OGTTs) for >23,000 pregnancies from 9 different countries around the world (1). The adverse pregnancy outcomes evaluated included birth weight >90th percentile (large for gestational age), fetal hyperinsulinemia, primary cesarean section, neonatal hypoglycemia, neonatal adiposity, shoulder dystocia, and preeclampsia. All adverse outcomes were related directly and significantly to the glucose concentration at each OGTT time point, but there was no obvious inflection point in any of the curves. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) undertook a process to reach consensus on the diagnostic criteria for GDM with respect to their value for predicting adverse pregnancy outcomes and recommended that GDM be diagnosed when one or more of the following plasma glucose values in the 75-g, 2-h OGTT was met or exceeded: fasting, 92 mg/dL (5.1 mmol/L); 1 h, 180 mg/dL (10 mmol/L); 2 h, 153 mg/dL (8.5 mmol/L) (2). According to the HAPO Study data, patients with GDM have an approximate doubling of the likelihood of a baby with a birth weight above the 90th percentile, 2.6 times the likelihood of fetal hyperinsulinemia, twice the likelihood of preeclampsia, and a 40% increase in the likelihood of shoulder dystocia and/or birth injury, compared with pregnancies without GDM (2) (Table 1). Admissions to the neonatal intensive care unit also were more common with GDM (9.1% vs 7.8%). The use of the same GDM criteria by caregivers throughout the world makes it possible to compare trends across populations and over time with respect to this condition and to apply results obtained from research in one setting to patients in another setting. Thus far, the IADPSG recommendations have been adopted by the American Diabetes Association, as well as by professional organizations in Japan and Germany, and are being considered throughout the world. At the time of this writing, the American Congress of Obstetricians and Gynecologists has recommended against changing previous practice (3).

Several concerns have been raised about these recommended criteria for the diagnosis of GDM.

The IADPSG Criteria Will Likely Diagnose GDM in 16%–18% of US Pregnancies. How Can Any “Disease” Afflict Such a High Proportion of Pregnant Women?

Epidemiologic studies have demonstrated a marked increase in the proportion of US births complicated by diabetes or GDM (4). This increase reflects the epidemic of type 2 diabetes and prediabetes outside of pregnancy. Data from the National Health and Nutrition Examination Survey demonstrate that from 2005 to 2008, 4.5% of women between 18 and 44 years of age had diagnosed or undiagnosed diabetes, and an additional 26.4% had prediabetes (impaired fasting glu-
cose, impaired glucose tolerance), for a total of 30.9% of women with disorders of glucose metabolism (C. Cowie, National Institute of Diabetes and Digestive and Kidney Diseases, personal communication, March 2, 2012). If one takes into account the first-trimester decrease in fasting glucose, the new GDM criteria appear remarkably similar to the criteria for prediabetes outside of pregnancy, and thus it should not be surprising that 16%–18% of pregnant women have a condition that is present in 31% of nonpregnant women of similar age.

The HAPO Study Was an Observational Study, Not a Treatment Trial. How Do We Know That Intervention Will Prevent the Excess Adverse Outcomes?

There have been 2 recent randomized single-blinded trials of identification and treatment of mild GDM. In one of the trials, mild GDM was defined as a 100-g, 3-h OGTT value meeting the lower of 2 alternative sets of criteria recommended by the American Congress of Obstetricians and Gynecologists but with a fasting plasma glucose concentration \( \leq 95 \text{ mg/dL} \) (\( \leq 5.3 \text{ mmol/L} \)) (5). Identification and treatment lowered by half the rates of macrosomia, primary cesarean section, shoulder dystocia, and preeclampsia; neonatal fat mass also was reduced by 37 g. All of these differences were statistically significant. The prevalence of these adverse outcomes among the unidentified, untreated individuals with GDM was similar to that in the HAPO Study participants, also unidentified and untreated, who would have met the new GDM criteria. In the other study (6), mild GDM was defined as a 2-h, 75-g OGTT value between 140 mg/dL (7.8 mmol/L) and 198 mg/dL (11 mmol/L) and with a fasting plasma glucose value \(< 140 \text{ mg/dL} \) [mean (SD) fasting glucose concentration, 86 (12) mg/dL, or 4.8 (0.67) mmol/L]. Identification and treatment reduced the likelihood of “serious complications” (death, shoulder dystocia, bone fracture, nerve palsy) by 66%. Macrosomia was reduced by 50%, and preeclampsia by 30%. The cesarean section rate was unchanged. Individuals with GDM who were identified and treated were more likely to have labor induced, and their babies were more likely to be admitted to the neonatal intensive care unit. Diagnostic criteria were, if anything, a little lower [2-h value \( \geq 140 \text{ mg/dL} \) \( (\geq 7.78 \text{ mmol/L}) \)] than the IADPSG recommendations [2-h value \( \geq 152 \text{ mg/dL} \) \( (\geq 8.44 \text{ mmol/L}) \)], each with an upper limit for inclusion of approximately 200 mg/dL (11.1 mmol/L). Both randomized trials are applicable to the new criteria.

The Identification and Treatment Trials All Found Individuals via a 2-Step Screening Process, whereas the New Recommendations Are for a 1-Step Process

These results may not be applicable. It has been suggested that GDM patients identified via a 2-step process (screening test and then a diagnostic test) may not be comparable with those identified via a 1-step process (diagnostic test only) (7). One possible concern might be that GDM patients identified by a 2-step process are at higher risk for adverse outcomes because they “failed” 2 tests. In fact, HAPO Study participants who would have had GDM according to the new criteria had adverse outcomes that were very similar to those of unidentified and untreated individuals identified via a 2-step process in a randomized trial (5).

Applying the Diagnostic Test to All Pregnant Women Is More Expensive than the 2-Step Process in Which a Screening Test Identifies Individuals Needing a Diagnostic Test

A cost-minimization analysis compared 2-step tests that used a 50-g challenge followed by a 75-g or 100-g OGTT, with a 1-step process that used the 75-g OGTT.

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Table 1. Morbidities increased in patients with GDM by the new criteria.a

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal in 75-g, 2-h OGTT</th>
<th>GDM (IADPSG proposed criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGAb (birth weight &gt;90th percentile)</td>
<td>8.3%</td>
<td>16.2%</td>
</tr>
<tr>
<td>Fetal hyperinsulinemia (cord C-peptide &gt;90th percentile)</td>
<td>6.7%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Neonatal adiposity (percentage body fat &gt;90th percentile)</td>
<td>8.5%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>4.5%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Shoulder dystocia/birth injury</td>
<td>1.3%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

*Adapted from Table B of the online appendix to the IADPSG recommendations on the diagnosis and classification of hyperglycemia in pregnancy [IADPSG(2)]. All differences are significant at a P value of <0.01 or better. b LGA, large for gestational age.
only. This analysis found that the 1-step process was the most expensive (Can$108 per patient tested vs Can$92 per patient tested), owing to more blood draws and the time required for the full 2-h OGTT on all women (8). The methods, however, identified similar proportions of the population as having GDM (3.6%–3.7%), because the WHO criteria for GDM were used in the 1-step test. Had the IADPSG diagnostic criteria been used, on the assumption of a 16% likelihood of GDM, the cost per diagnosed case would have decreased by 75% for the 1-step process, although the cost per patient tested would not have changed.

Even These New Criteria Predict Only a Minority of Macrosomic Babies; Most Large Babies and Babies with Shoulder Dystocia and Other Adverse Outcomes Are Born to Mothers with Normal Glucose Tolerance

This argument has been advanced (7, 9) as a reason not to use the new recommendations; however, that all large babies are pathologically large and that limiting all growth would be beneficial has never been claimed. The underlying principle supporting identification and treatment of GDM is that fetal hyperinsulinemia leads to increased fat deposition and that infants of diabetic mothers not only are large but also are overly fat. Numerous studies have demonstrated that, at a given birth weight, infants of diabetic mothers are more likely to experience shoulder dystocia than are infants of nondiabetic mothers. HAPO Study data have demonstrated that fetal hyperinsulinemia, increased neonatal fat, and being large for the gestational age all were associated with a higher maternal glucose concentration at a mean of 28 weeks’ gestation. The assertion that only a small proportion of large babies will be predicted and possibly be prevented by identifying and treating GDM is true, but that is not a valid reason to reject the new recommendations. Indeed, if it were, then one could argue that the previous approach should also be abandoned because it identified an even smaller proportion of the adverse outcomes.

The Cost to Society of Identifying 16%–18% of Pregnancies as GDMs Is Difficult to Justify

An increase in the proportion of pregnancies in which GDM is diagnosed will undoubtedly present a challenge to our healthcare systems. It is somewhat reassuring that in the 2 randomized trials of identification and treatment of mild GDM (5, 6), only 8% and 20% of such cases required the use of insulin. Nevertheless, it will be important to develop more-efficient methods of care for patients with mild GDM. Group patient education may be helpful. Better ways of identifying individuals with GDM who require fetal testing will save resources. There is evidence that self-monitoring of blood glucose at a frequency less than daily may be feasible (10). A cost–benefit analysis carried out on data from the Australian Carbohydrate Intolerance Study of Pregnant Women (ACHOIS) study (11) showed that for every patient diagnosed and treated for mild GDM (compared with undiagnosed individuals), there was an incremental A$539 in inpatient and outpatient hospital costs, with A$65 in additional charges to patients and their families. The cost–benefit ratio was A$27 503 per serious perinatal complication prevented and A$60 506 per perinatal death prevented. The authors considered the incremental cost per extra life-year to be highly favorable. A decision analysis demonstrated that the IADPSG recommendations are cost-effective when postdelivery care to prevent future diabetes is included (12).

The IADPSG recommendations for diagnosing GDM, which have already been endorsed by the American Diabetes Association, should be used worldwide, because they are based on their value for predicting pregnancy outcomes and have been shown to identify high-risk pregnancies in which adverse outcomes can be prevented by reasonably simple interventions.

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