In the US, the most common practice for gestational diabetes mellitus (GDM)\(^2\) screening is a 2-step process: an initial 1-h (50 g) glucose tolerance test (GTT) done at 24–28 weeks, followed by a confirmatory 3-h (100 g) GTT (fasting, 1-h, 2-h, and 3-h measurements) \(\text{(1)}\). On the assumption of a 1% rate of pre-GDM and the fact that 10% of pregnant women will be of “low risk” and thus not require screening, approximately \(3.6 \times 10^6\) women undergo GDM screening per year in the US \(\text{(2)}\). A diagnosis of GDM is then made if \(\geq 2\) values on the 3-h GTT are above reference limits \(\text{[Carpenter and Coustan criteria: fasting, } >95 \text{ mg/dL (} >5.27 \text{ mmol/L); } 1 \text{ h, } >180 \text{ mg/dL (} >9.99 \text{ mmol/L); } 2 \text{ h, } >155 \text{ mg/dL (} >8.60 \text{ mmol/L); } 3 \text{ h, } >140 \text{ mg/dL (} >7.77 \text{ mmol/L).}}\) With the current American College of Obstetricians and Gynecologists (ACOG) diagnostic criteria, approximately 7% of pregnant women are diagnosed with GDM (>250 000 women per year).

Although there was a time when many experts questioned whether GDM was a “disease” that warranted treatment, data from 2 randomized clinical trials (RCTs) that demonstrated both maternal and neonatal benefit from treatment for GDM have largely quieted this argument \(\text{(3, 4)}\). Although the National Institute of Child Health and Human Development (NICHD) Maternal Fetal Medicine Units Network (MFMU) mild GDM treatment trial did not report differences between groups in the primary composite outcome (stillbirth or neonatal death, hypoglycemia, hyperbilirubinemia, increased cord blood C-peptide, and birth trauma) or between any of the individual outcomes in the composite, there were statistically significant differences in several secondary outcomes, such as macrosomia [number needed to treat (NNT) = 12], shoulder dystocia (NNT = 40), cesarean delivery (NNT = 15), and preeclampsia (NNT = 34).

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated a continuous association of maternal glucose concentrations with adverse pregnancy outcomes (e.g., cesarean delivery, birth weight >90th percentile, clinical neonatal hypoglycemia, and fetal hyperinsulinemia) \(\text{(5)}\). The HAPO study used a 1-step 75-g GTT (fasting, 1-h, and 2-h measurements). On the basis of the HAPO results, an expert group, the International Association of Diabetes and Pregnancy Study Group (IADPSG), has suggested that GDM screening be performed with the 1-step 75-g GTT and a diagnosis of GDM be made if one or more values are above designated reference thresholds [fasting, >92 mg/dL (>5.11 mmol/L); 1 h, >180 mg/dL (>9.99 mmol/L); 2 h, >155 mg/dL (>8.49 mmol/L)] \(\text{(6)}\). These thresholds for GDM diagnosis are much lower than current diagnostic criteria used for GDM in the US and recommended by the ACOG. If these thresholds are adopted, it is estimated that the overall prevalence of GDM will be 17.8% in the US (>640 000 women per year). This change in the standard of practice has been proposed by the IADPSG and has been endorsed by the American Diabetes Association, but not by ACOG.

There is one fundamental reason why the evidence is insufficient to change our current practice: The HAPO study was observational in design and cannot provide information regarding the effectiveness of treatment of women with “increased” glucose concentrations that are lower than current thresholds for GDM diagnosis. It is unknown whether treatment (nutritional modification and glucose monitoring) for women with this level of glycemia would (a) decrease glucose concentrations and/or (b) improve perinatal outcomes.

Certainly there are some (rare) situations in which an observational study can provide information regarding treatment effectiveness \(\text{(7, 8)}\), but the medical literature is replete with examples of a therapy that was...
assumed from observational study to have benefit but was later proved ineffective (or even harmful) when tested in a rigorous RCT (e.g., hormone replacement therapy in women to prevent cardiovascular disease, chemotherapy and bone marrow transplantation for metastatic breast cancer, repeat antenatal corticosteroids administered to women threatened with preterm birth, antibiotics to treat asymptomatic bacterial vaginosis to prevent preterm birth) (9). That is why RCTs, rather than observational studies, are essential for answering most questions regarding therapy.

If the HAPO criteria were adopted in the US, it is most likely that the majority of the approximately additional 10% of pregnant women designated as having GDM would require nutritional modification and glucose monitoring only, rather than progressing to insulin or oral hypoglycemic agents (given that they would have “milder” hyperglycemia). It is unknown whether treatment of these women would affect their glycemic status substantially and/or influence the frequency of adverse outcomes (e.g., cesarean delivery, birth weight >90th percentile, clinical neonatal hypoglycemia, and fetal hyperinsulinemia). These women by definition are “milder” in their glucose intolerance than those in the NICHD Mild Gestational Diabetes Mellitus Study. Given their “milder” state of glucose intolerance, it is also less realistic to posit a magnitude of treatment effect similar to that obtained in this RCT. A population that would be most similar to these women would be overweight or obese women without diabetes mellitus. RCTs involving overweight and/or obese women without diabetes mellitus have tested dietary modification and moderate exercise to limit excessive gestational weight gain (10). A recent systematic review of 13 studies reported a decrease in maternal gestational weight gain and cesarean delivery but found no impact on neonatal birth weight or any infant health outcome (11). Despite the associations from observational studies regarding increased rates of adverse perinatal outcomes in obese women, there is a lack of level I evidence to support the hypothesis that treatment of these women improves fetal/neonatal outcomes.

Some experts have argued that nutritional modification (with daily glucose monitoring for some period of time) poses little risk of harm to the mother and fetus, because these interventions are “benign.” There is potential, however, for indirect patient harm due to the designation of having GDM (and thus being labeled as having a “high risk” pregnancy). A GDM diagnosis increases the overall use of healthcare services, leading to additional prenatal visits as well as the increased discomfort, inconvenience, and costs associated with daily blood glucose monitoring (12). In a secondary analysis of the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), women in the intervention group had much higher antenatal and inpatient costs, and higher frequencies of labor inductions and admissions to the neonatal nursery. Additionally, the diagnosis of GDM in real-world practice will lead to the overuse of tests and, potentially, other unnecessary therapies, such as additional ultrasound examinations for fetal growth assessment, additional laboratory testing, higher rates of labor induction, and a lower threshold of cesarean delivery. Thus, these additional risks and costs would have a major public health impact, given that the change in diagnostic criteria would lead to an additional 390,000 new GDM pregnancies per year.

In summary, a change in the diagnostic criteria for GDM from current ACOG guidelines to those suggested by the IADPSG would cause a massive expansion of treatment, which could be justified only after obtaining level I evidence regarding treatment benefit, potential harms, and costs. It is neither surprising nor uncommon for an expert specialty group to advocate for the greater importance and priority of their disease or condition of interest; however, authors of evidence-based treatment guidelines and societal policy makers should be resolute that only well-conducted interventional trials dictate such a huge paradigm shift in care. Making such a change in practice on the basis of biological plausibility, observational studies, and expert opinion is fraught with potential for unintended consequences.

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