Do We Know How to Find Gestational Diabetes Mellitus?

It is now a common practice to identify women with gestational diabetes mellitus (GDM) and initiate treatment aimed at preventing hyperglycemic episodes and improving outcome for the woman and her unborn child (1-3). However, since before the 1st Workshop Conference on Gestational Diabetes Mellitus in 1979 (4), there has been heated discussion about how this is best done. By the 4th international workshop in 1997 (5), a compromise was agreed on that either of 2 protocols would be acceptable. The first protocol was to continue the previously recommended 50-g glucose challenge test with a diagnostic 3-h 100-g oral glucose tolerance test (OGTT) if the glucose concentration was increased at 1 h after the 50-g load. A diagnosis of GDM required that glucose thresholds be met or exceeded at 2 or more of the 4 time points during the 100-g test. In 1997, the only change to this protocol was that the cutoffs for glucose concentrations at each of the 4 time points were lower than previously recommended to reflect more accurately the change from measuring glucose in whole blood to measuring it in plasma (6). The second protocol was to administer a 2-h 75-g OGTT and, using the same glucose thresholds, a diagnosis was to require meeting or exceeding the thresholds at 2 or more of the 3 time points. The 5th International Workshop Conference, held in November 2005, did not address the issues of screening and diagnosis of gestational diabetes, but the conference participants recommended endorsing the recommendations from the 4th Workshop (personal communication, Planning Committee Chair, 5th International Workshop-Conference on Gestational Diabetes, November, 2005, Chicago).

Mello et al. (7) show in this issue of Clinical Chemistry that the 2 protocols do not yield the same result, although it is not known if women who were missed with the 75-g load but identified with the 100-g load in early pregnancy might have been identified at 26 to 31 weeks—the time when screening for GDM is traditionally performed. In this study, no data are presented on the concordance of the 2 testing procedures in women with entirely normal glucose tolerance because this group of women did not participate in the 100-g 3-h test.

It is not surprising that 2 different protocols used for testing on 2 different days yield different results. It has been known for decades that, among nonpregnant adults with healthy glucose tolerance, a higher glucose load leads to a higher insulin response, leading to similar glucose concentrations while among those with some degree of glucose intolerance, who probably also have some degree of β-cell failure, the higher load leads to higher postload concentrations (8, 9). GDM is an exaggeration of the expected glucose intolerance of pregnancy and, although it hasn’t been reported from a systematic study, women with the glucose intolerance of GDM would be expected to have higher glucose concentrations after a 100-g load than they would after a 75-g load. According to the summary and recommendations of the 4th international workshop conference on gestational diabetes, the cutoff concentrations for the 75-g test were selected to represent the mean plus 1.5 SDs of the OGTT concentrations in the study of Sacks et al. (10). However, to make the concentrations consistent with those of the 100-g test, the 1-h concentration from the Sacks study, which calculated to 178 mg/dL (9.9 mmol/L), was arbitrarily raised to 180 mg/dL (10 mmol/L), and the 2-h concentration, which calculated to 145 mg/dL (8.1 mmol/L) was increased to 155 mg/dL (8.61 mmol/L)—an increase of 6.5%. In addition, with the 100-g test, a diagnosis of GDM is made if only half of the measured glucose concentrations meet or exceed the respective thresholds while the 75-g test requires two thirds of the concentrations to meet or exceed the thresholds. If the 100-g 3-h OGTT is to be considered the gold standard, then the concentrations required for the 75-g 2-h test are clearly too high and the methodology too restrictive. This was demonstrated very nicely by Mello’s article in this issue. There is, however, strong skepticism on the validity of the 100-g OGTT even after the thresholds have been revised downward. Perhaps it’s time to consider an entirely different approach to identifying women who are at risk of GDM, an approach that neither relies on a single glucose test, as in the 75-g OGTT, nor requires a woman to fail both a glucose challenge test and the 100-g OGTT.

We may be asking the wrong question with the wrong tool to identify pregnant women at risk for complications. If the outcome variable is the health of the fetus and neonate, then the question should be, “What test identifies women at risk for diabetic fetopathy (macrosomia and neonatal metabolic aberrancy)?” (11). Previous studies reported that mixed meal tolerance tests were more suitable for screening and for diagnosing maternal hyperglycemia than an artificial situation such as that of the OGTT (i.e., drinking a glucose solution) (12-14). However, the meal test was not endorsed by any of the expert committees and thus was not further validated beyond the initial reports. Now that we have continuous glucose sensing available, perhaps we should apply this new technology to the screening and diagnostic tests (15). The universal acceptance of the 1-h delay between the consumption of the drink and the first glucose concentration measurement is not based on scientific data but is merely “tradition”, and there may be other time points that better identify the high risk pregnancy (16). The area under the curve of a continuous glucose profile for 3 h may be a better metric. Alternatively, continuous glucose monitoring in the typical home setting for several days may better reflect the ambient glucose that impacts on fetal growth, development, and metabolism. Until we are able to relate the screening and diagnostic tool to pregnancy outcome rather than to standard deviations above the mean glucose, we shall always have a debate. It is time to reassess
the question and ask “What test best identifies glucose toxicity for the fetus?”

References


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DOI: 10.1373/clinchem.2006.071704