Diagnosing GDM in the first trimester

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December 2019—"If you thought that diagnosing gestational diabetes at 24 to 28 weeks was unsettled, you haven't seen anything yet."

That was David B. Sacks, MB, ChB, of the National Institutes of Health, speaking this year in the AACC session on gestational diabetes mellitus (GDM) with his co-presenters who debated the use of the one-step and two-step methods for diagnosing GDM in the second and third trimesters. His talk: "Let's Not Wait: Diagnosing GDM in the First Trimester."

"Why do we need to identify gestational diabetes in the first trimester?" asked Dr. Sacks, senior investigator and chief of the clinical chemistry service in the Department of Laboratory Medicine, NIH. "Hyperglycemia in late pregnancy leads to adverse outcomes. It's thought that women with early gestational diabetes are at higher risk for complications," Dr. Sacks said, "and it's also thought that early therapy would be beneficial. This has clearly been shown for pregnant women with preexisting diabetes, and these are women who have diabetes already who became pregnant."

A study published this year that looked at adverse outcomes in women with preexisting diabetes showed an odds ratio of 3.5 for preeclampsia and cesarean delivery, he said (Alexopoulos AS, et al. *JAMA.* 019;321[18]:1811–1819). The odds ratios are increased for all the child adverse outcomes, ranging from about 1.9-fold to almost 27-fold. Most are between a three- and four-fold odds ratio.

Dr. Sacks

The first trimester is when fetal development is most rapid and "when the majority of the fetus' organ systems are at risk," yet the current screening recommendation for GDM is at 24 to 28 weeks. "We're missing almost two-thirds of the pregnancy," Dr. Sacks said, and there are now recommendations for screening for diabetes early in pregnancy.

Several organizations, among them the American Diabetes Association, American College of Obstetricians and Gynecologists, Diabetes Canada, and World Health Organization, have identified selected populations in which screening should be done early in pregnancy, he said, adding, "The guidelines are very different." (Johns EC, et al. *Trends Endocrinol Metab.* 2018;29[11]:743–754.) Diabetes Canada recommends early screening for one population, while ACOG lists nearly a dozen populations.

The ADA and WHO have the same recommendations, which are, for women with risk factors, to evaluate for undiagnosed diabetes at the first prenatal visit (first trimester) using the standard diagnostic criteria: increased hemoglobin A1c, increased fasting glucose, or a two-hour glucose tolerance test, Dr. Sacks said. "If this is positive, the mother is diagnosed with diabetes in pregnancy." If the result is negative, the mother should be screened for gestational diabetes at 24 to 28 weeks.

Hyperglycemia in pregnancy is divided into two groups: diabetes in pregnancy or GDM, and either one can be type one or two. Diabetes in pregnancy can be diagnosed before the start of pregnancy, even during childhood years, or during pregnancy for the first time.

Women diagnosed with GDM early are more likely to have adverse outcomes. “Maternal outcomes for GDM diagnosed in the first trimester are similar to those with preexisting diabetes,” Dr. Sacks said (Sweeting AN, et al. *Diabetes Care.* 2016;39[1]:75–81). Similar to the maternal complications, the neonatal complications are significantly higher when the gestational diabetes is diagnosed earlier. “That raises the question as to how we predict gestational diabetes in the first trimester,” Dr. Sacks said.

For biochemical predictors, “People have looked at glucose, either fasting, oral glucose tolerance test, or even continuous glucose monitors. They’ve looked at different kinds of glycated proteins, inflammatory markers, insulin resistance markers, placenta-derived markers, adipocyte-derived markers—the list goes on,” he said. Judging by the literature, most of the evidence has been directed toward fasting plasma glucose and glycated proteins in the first trimester, Dr. Sacks said.

A 2009 study found a progressive increase in adverse maternal and fetal outcomes with increasing fasting plasma glucose in the first trimester (Riskin-Mashiah S, et al. *Diabetes Care.* 2009;32[9]:1639–1643).

The IADPSG initially recommended a fasting plasma glucose ≥92 mg/dL (5.1 mmol/L) in early pregnancy as diagnostic of GDM, Dr. Sacks said, but these criteria were not derived from data in the first half of pregnancy. “The study measured glucose at 24 to 28 weeks, so the diagnosis of gestational diabetes in early pregnancy by fasting glucose or OGTT is not evidence based. There is no evidence at all.”

The only evidence critical to this discussion is that “fasting plasma glucose at the first antenatal visit is not always consistent with fasting plasma glucose at 24 to 28 weeks,” Dr. Sacks said, referencing a study of 13 hospitals in China (Zhu WW, et al. *Diabetes Care.* 2013;36[3]:586–590). “The average of the first visit for these data was about 13.4 weeks, and it is a very large study, more than 17,000 individuals.”

With the cutoff of 92 mg/dL, “the sensitivity in this study showed subsequent gestational diabetes was only 0.24,” Dr. Sacks said. “The specificity was better, 0.92, but the positive predictive value was only 0.39.”

What is unknown about glucose in early pregnancy is whether glucose concentrations in women with GDM increased in early pregnancy, and, if so, when is the onset of maternal hyperglycemia. How soon after conception?

Data from the same study in China show the fasting plasma glucose level drops substantially from five weeks of gestation to just over 20 weeks.
Other unknowns: Are the current GDM diagnostic criteria for glucose valid before 24 weeks of gestation, and, if not, what cutoff values should be used?
A study conducted in New Zealand found that an HbA1c threshold of 5.9 percent was the best predictor of GDM at less than 24 weeks of gestation (Hughes RCE, et al. *Diabetes Care.* 2014;37[11]:2953–2959).

As with fasting plasma glucose, HbA1c is complicated, Dr. Sacks said. Data published in 2018 by Cuilin Zhang, MD, PhD, MPH, senior investigator, National Institute of Child Health and Human Development, Division of Intramural Population Health Research, NIH, showed changes in HbA1c concentrations at four different stages of pregnancy: enrollment (eight to 13 weeks of gestation), first study visit (16 to 22 weeks of gestation), second study visit (24 to 29 weeks of gestation), and just before delivery (34 to 37 weeks of gestation) (Hinkle SN, et al. *Sci Rep.* 2018;8[1]:12249). HbA1c concentrations fell between enrollment and the first study visit, then rose through the final study visit. This happens in women diagnosed with GDM and in those who did not subsequently develop GDM. “But at all time periods, HbA1c is higher in the women who subsequently develop gestational diabetes,” Dr. Sacks said.
Dr. Zhang and colleagues found that the optimal HbA1c threshold for diagnosing GDM in the first trimester was 5.7 percent, slightly lower than the 5.9 percent cutoff reported in the New Zealand study.

The diagnostic value of glycated albumin, which represents average glycemia over the preceding 14 to 21 days, has also been considered. “In theory, it is potentially useful in diagnosing gestational diabetes including the first trimester,” Dr. Sacks said, though further studies are needed.

The unknown issues regarding glycated proteins in early pregnancy are as follows: What are the reference intervals for HbA1c and glycated albumin in pregnancy, are these tests realistic alternatives to glucose measures for early diagnosis of GDM, is the predictive value of HbA1c for GDM useful in early pregnancy, and does HbA1c and/or glycated albumin predict adverse outcomes in GDM?

“The important question is, does predicting gestational diabetes in the first trimester make a difference? As of August 2019,” Dr. Sacks said at the meeting, “the answer is, Who knows? Nobody knows.”

He cited four limitations of the data on early identification of GDM, the first of which is that no criteria had been validated. Second, in most of the published studies, the outcome is usually GDM at 24 to 28 weeks, “but not maternal or fetal outcomes, which is the important question.” Third, there is no consensus on whether one should test or how to test, and, fourth, there is no evidence that testing has clinical value, “which at this stage is the important issue.”

The National Institute of Diabetes and Digestive and Kidney Diseases published an executive summary of a workshop that examined research gaps in GDM (Wexler DJ, et al. *Obstet Gynecol.* 2018;132[2]:496–505). It identified two gaps: therapy and early pregnancy diagnosis and treatment. “Clearly, this has been identified by the NIH as a very important topic,” Dr. Sacks said.

At the workshop, unanswered questions were identified: Which techniques should be used to identify GDM in early pregnancy? Is diagnosis of GDM early in pregnancy of clinical value? Will identification and/or treatment of GDM in early pregnancy improve outcomes for the mother and baby? Several studies of early diagnosis and/or treatment of GDM are ongoing, he said, “so presumably these questions will be answered in the not-too-distant future.”

Dr. Sacks’ take-home message: There is no consensus or evidence regarding the important issues surrounding predicting GDM early in pregnancy, which are how to identify individuals with GDM in the first trimester and whether prevention or treatment is effective. The latter is the key question, he said, and “until it can be answered, it will be hard to justify screening.” And last: Can it make a difference in outcome?

Amy Carpenter Aquino is CAP TODAY senior editor. The GDM session was also presented at the American Diabetes Association annual meeting in June.