For gestational diabetes, one step or two?

Amy Carpenter Aquino

December 2019—The controversy surrounding the approved methods for screening gestational diabetes mellitus took the form of a debate at this year's AACC annual meeting, with two speakers defending the one-step or two-step method.

Florence M. Brown, MD, assistant professor of medicine at Harvard Medical School and co-director of the diabetes in pregnancy program at the Joslin Diabetes Center and Beth Israel Deaconess Medical Center, Boston, favors the use of the one-step International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria to detect GDM.

"My position today is we should use the one-step IADPSG criteria to detect gestational diabetes," Dr. Brown said. Her institution began using the criteria shortly after they were published in 2011 but returned to the two-step criteria after the American College of Obstetricians and Gynecologists reaffirmed its position to use the two-step method in a 2013 practice bulletin "That continues to be the case."

Dr. Brown presented the case of a 33-year-old pregnant woman with a prior history of gestational diabetes. The patient was referred to Dr. Brown because of an elevated amniotic fluid level, a fetal abdominal circumference greater than the 90th percentile, and a one-hour glucose loading test (GLT) of 151 mg/dL at 31 weeks of gestation. She had passed two other GLT tests earlier in pregnancy.

"She had pronounced fasting hyperglycemia, which the glucose load tolerance screen did not pick up," Dr. Brown said. The patient's fasting blood sugar level was greater than 110 mg/dL and she had additional risk factors for GDM: a strong family history of type two diabetes and obesity with a BMI of 39. "She was counseled on lifestyle management and management with ongoing titration of insulin for the remainder of her pregnancy."

"Even though the obstetrician had done the ACOG-recommended screening for this patient, why do a screening test on somebody who already has a 50 percent chance of developing gestational diabetes just on the basis of having had gestational diabetes in her previous pregnancy?" she asked.

GDM diagnosis is controversial because of the differences between the two screening methods, Dr. Brown said. The two-step method involves a nonfasting one-hour 50-g GLT. If the result is positive, the GLT is followed by a diagnostic fasting three-hour 100-g oral glucose tolerance test, with values checked at fasting and one, two, and three hours. GDM is diagnosed if there are two or more abnormal values. "The thresholds that are currently in use are the NDDG [National Diabetes Data Group] or the Carpenter and Coustan criteria," Dr. Brown said. ACOG, the National Institutes of Health consensus conference, and the American Diabetes Association endorse the two-step method.

Dr. Brown

The ADA also endorses the one-step IADPSG screening criteria, which is a single diagnostic fasting 75-g two-hour OGTT, with blood sugars checked at fasting, one hour, and two hours, she said. GDM is diagnosed if one or more values is positive. The Endocrine Society, World Health Organization, and International Federation of Gynecology and Obstetrics endorse the one-step method.

That the ADA endorses the two-step method with two different sets of thresholds and the one-step method with one set of thresholds "is very confusing and we need consensus," Dr. Brown said.

The two-step method got its start in a 1964 study of 752 pregnant women who received a 100-g three-hour OGTT with whole blood samples checked at fasting and one, two, and three hours (O'Sullivan JB, et al. *Diabetes.* 1964; 13:278–285).

"The glucose thresholds they chose were two standard deviations above the mean of 97.7th percentile, and they required two abnormal values," she said. "They had been following a group of women who had been getting a glucose tolerance test routinely, and they applied these thresholds to these women." Eight years after they were diagnosed with GDM, 29 percent of the women had developed type two diabetes. At 16 years it was 60 percent. "The gestational diabetes prevalence, based on the thresholds they chose, was 2.5 percent, at a time when the diabetes prevalence in the United States was just 1.24 percent."

In 1973, the authors recommended a nonfasting 50-g glucose loading test to identify high-risk women in a very low prevalence population. The threshold was a one-hour whole blood glucose of 130 mg/dL, and with that they had 80 percent sensitivity. "Later, a one-hour plasma threshold of 140 mg/dL was found to have approximately the same sensitivity," Dr. Brown said.

"At a time when the prevalence of gestational diabetes was 2.5 percent, a false-negative rate of 20 percent was acceptable at an absolute of 0.5 percent."

The diagnostic 100-g OGTT thresholds now are the NDDG and the Carpenter and Coustan criteria for measuring plasma, and two abnormal values are needed for a GDM diagnosis.

Dr. Brown posed two questions to help determine whether there is a benefit to treating GDM: Does treatment of mild gestational diabetes reduce adverse outcomes, and are adverse outcomes in pregnancy independently related to maternal hyperglycemia, or are other factors—such as maternal BMI or age—the main drivers?

The Australian Carbohydrate Intolerance Study in Pregnant Women (24 to 34 weeks' gestation) trial addressed whether treatment of mild GDM makes a difference in fetal and maternal health (Crowther CA, et al. *N Engl J Med.* 2005;352[24]:2477–2486). The two-step inclusion criteria were an abnormal 50-g glucose loading test (≥140 mg/dL) or risk factors, and a 75-g OGTT with a two-hour value ≥140 mg/dL. Women with fasting glucose levels ≥140 mg/dL, or a two-hour value on the 75-g OGTT ≥198 mg/dL, were excluded because they were considered to have diabetes.

Treating women for GDM was found to lead to fewer composite serious perinatal outcomes and diminished depression at 12 months postpartum. Reductions were seen in birth weight and in rates of infants who were large for gestational age and had macrosomia. The rate of induction of labor increased.

The Maternal-Fetal Medicine Units Network study of nearly 960 women addressed the same question (Landon MB, et al. *N Engl J Med.* 2009;361[14]:1339–1348). Inclusion criteria began with a one-hour GLT with a value of 135–199 mg/dL. Women who met that threshold then had a three-hour 100-g OGTT in which a fasting glucose result of <95 mg/dL and two or three abnormal values above the thresholds of a one-hour 180 mg/dL, a two-hour 155 mg/dL, or a three-hour 140 mg/dL would be considered mild gestational diabetes. "These would be the Carpenter and Coustan thresholds," Dr. Brown said.

The MFMU Network study found reductions in birth weight, macrosomia, and fat mass in women treated for GDM, in addition to a lower prevalence of cesarean delivery, lower frequency of shoulder dystocia, and reductions in preeclampsia and gestational hypertension.

So the answer to the question of whether treatment of mild GDM reduces adverse outcomes is yes, Dr. Brown said.

Are adverse outcomes in pregnancy independently related to maternal hyperglycemia or are other factors, such as BMI or age, the main drivers? Here Dr. Brown referenced the Hyperglycemia and Adverse Pregnancy Outcome

(HAPO) study (*N Engl J Med.* 2008;358[19]:1991–2002). More than 23,000 women underwent a 75-g OGTT between 24 and 32 weeks of gestation (fasting and one and two hours). The primary outcomes evaluated across different increasing glucose categories were birth weight greater than the 90th percentile, primary cesarean section, clinical neonatal hypoglycemia, and cord-blood serum C-peptide level greater than the 90th percentile. "For all these adverse outcomes," she said, "there is a linear relationship between the adverse outcomes and the glucose levels."

There was a similar linear relationship between fasting, one-hour, and two-hour glucose levels and the secondary adverse outcomes: premature delivery, shoulder dystocia, hyperbilirubinemia, preeclampsia, and a need for intensive neonatal care.

"And these associations of the primary and secondary outcomes with glucose were independent of BMI," Dr. Brown said, so, yes, "adverse outcomes in pregnancy are independently related to maternal hyperglycemia."

The IADPSG convened an international consensus conference in 2008 with the goal of using the HAPO study outcomes data to determine thresholds for a glucose tolerance test (*Diabetes Care.* 2010;33[3]:676–682).

"They chose neonatal outcomes: greater than 90th percentile for birth weight, body fat, and cord-blood C-peptide," Dr. Brown said. Conference members found linear relationships with these outcomes for maternal fasting, one-hour, and two-hour glucose across increasing levels of hyperglycemia. "So where do we draw the thresholds when this is a linear relationship? There's no inflection point to help us know where to make these thresholds."

"They had to draw the line somewhere," Dr. Brown continued, "so they recommended one-step testing for all pregnant women between 24 and 28 weeks of gestation," and that they be screened and diagnosed using a one-step fasting two-hour 75-g OGTT. The glucose thresholds were determined by choosing the glucose values when the odds ratio for the neonatal outcomes of HAPO were 1.75, compared with mean glucose values. Based on this odds ratio, the fasting level was 92 mg/dL (5.1 mmol/L), the one-hour level was 180 mg/dL (10 mmol/L), and the two-hour level was 153 mg/dL (8.5 mmol/L). One abnormal glucose level result was required for diagnosis.

The HAPO study clearly showed that women who had a normal glucose tolerance test rate based on IADPSG criteria had a lower frequency of all adverse outcomes compared with women who had one abnormal glucose value. "Every single one of these adverse outcomes was lower in women below the threshold compared to women who had one or more abnormal values," Dr. Brown said.

A HAPO follow-up study looked at long-term outcomes in more than 4,500 mothers and offspring 10 to 14 years after the HAPO study, with children and mothers undergoing a 75-g two-hour OGTT. The study found continuous linear associations between maternal glucose during pregnancy with childhood adiposity, skin-fold thickness, percent body fat, waist circumference, and markers of childhood glucose metabolism. "There is a strong relationship between the mother's metabolic status in pregnancy and the offspring's metabolic status 10 to 14 years later," Dr. Brown said (Scholtens DM, et al. *Diabetes Care.* 2019;42[3]:381–392).

When researchers dichotomized the subjects based on post hoc diagnosis of maternal GDM by IADPSG criteria, in which 14.3 percent of the mothers had GDM versus mothers who did not have GDM, "they found that children of those mothers were more likely to have impaired glucose tolerance, higher 30-minute, one-hour, and two-hour glucose levels on a 75-g two-hour OGTT, and reduced insulin sensitivity and oral disposition index," she said. The children also had higher odds ratio of obesity, body fat percent, waist circumference, and skin fold thickness than children of mothers who did not have GDM.

"For the mothers, the odds ratio was 3.44 for long-term diabetes or prediabetes," she said. "In terms of absolute numbers, 52 percent of the mothers who made criteria by IADPSG criteria had either diabetes or prediabetes, and 20 percent of mothers who did not have gestational diabetes had diabetes or prediabetes."

Dr. Brown referred to her published report of the prevalence of GDM by country, which showed that the IADPSG criteria "does definitely increase the prevalence of gestational diabetes" (Brown FM, et al. *Curr Diab Rep.*

2017;17[10]:85).

To sum up, she presented a comparison of the 1964 study of 762 patients at a single center, “at a time when the prevalence of diabetes was 1.24 percent,” with the HAPO studies, in which there were 23,000 women and more than 4,500 pairs in the follow-up from multiple centers across the globe. “Both demonstrated increased maternal risk for diabetes in the population, but only the one-step method looked at pregnancy, neonatal, and long-term offspring outcomes.”

Amy Valent, DO, a maternal fetal medicine specialist and assistant professor of obstetrics and gynecology, Oregon Health and Science University, and director of the OHSU diabetes in pregnancy program, defended the two-step method to screen for gestational diabetes.

“We have these two diagnostic methods, and they’re both appropriate per the guidelines of several of our major groups,” Dr. Valent said. “What will it take for us to change and choose one or the other?”

Dr. Valent said she advises her patients to think of their gestational diabetes diagnosis as “a crystal ball into your future metabolic health” because more than 50 percent of women with GDM develop type two diabetes in the five to 10 years after diagnosis.

Dr. Valent

She called the HAPO study a “wakeup call to providers to realize that women were at higher risk for adverse pregnancy outcomes—not necessarily type two diabetes—in the future, at lower glycemic targets than we previously thought. Before 2008, we didn’t have this recognition, and HAPO homed in on that to make us realize that even at lower glycemic ranges, women are still at higher risk.”

The one-step IADPSG criteria that uses the 1.75 odds ratio came out in 2010, and while the method increases the prevalence of GDM diagnoses, “the [2013] NIH consensus of experts didn’t think that the cost was justified with the potential improvement in outcomes,” she said. The U.S. Preventive Services Task Force, however, recognized through evidence that there was enough of a risk factor of GDM among women and in 2014 recommended universal screenings at 24 weeks of gestation.

“Where are we now?” she asked.

The two-step approach is a nonfasting 50-g oral glucose challenge test. “You can use the Carpenter-Coustan criteria of 135, but most institutions will use population-based prevalence to determine if they’re using a 130, 135, or 140 cutoff.”

Women who fail this step continue to the diagnostic standard of a fasting 100-g OGTT. The Carpenter and Coustan or the NDDG criteria, both of which use plasma, can be used.

An effective screening test must detect a condition in a high proportion of the population, be safe and reasonably cost-effective, and demonstrate improved health outcomes, Dr. Valent noted.

The two-step method, using the Carpenter and Coustan criteria, has demonstrated relatively good sensitivity between 85 and 99 percent, and a specificity between 77 and 86 percent, Dr. Valent said. “Of course, your population prevalence drives your positive predictive values, so that can vary. But it has very high negative predictive values” of 98 to 100 percent.

The two-step approach is more immediately cost-effective, she said, since the majority of women are not diagnosed with GDM. By increasing GDM diagnoses threefold, the one-step approach would result in increased interventions, maternal and neonatal evaluations, loss in productivity, and anxiety and stress for the patient. “We have to consider the costs of testing supplies and medications, clinic time, provider time, patient time, social work time, dietician, ultrasounds, and then antenatal surveillance because they are at a higher risk for stillbirth.”

Does the test identify a problem, and if the problem is treated, are the outcomes better? The Maternal-Fetal Medicine Units Network study demonstrated improved outcomes for mother and baby with treatment of mild GDM. A secondary analysis of the MFMU Network study demonstrated decreased rates of pregnancy-induced hypertension, macrosomia, and large-for-gestational-age neonates among women treated after diagnosis of GDM with Carpenter and Coustan or NDDG criteria, suggesting that using Carpenter and Coustan criteria, a more sensitive test than NDDG, has the ability to reduce maternal and neonatal risks and is more commonly used.

The Diabetes Prevention Program trial of the National Institute of Diabetes and Digestive and Kidney Diseases studied men and women at high risk for type two diabetes, and among them was a group of 350 women with a previous diagnosis of GDM, and 1,400 pregnant women who did not have diabetes in their pregnancies but had elevated BMI and impaired fasting glucose levels. Participants were randomized to receive either intense lifestyle intervention, metformin, or placebo. Women with a history of GDM who had lifestyle intervention or used metformin had similar reductions of 35 to 40 percent in the incidence of type two diabetes over 10 years, Dr. Valent said.

By identifying women during pregnancy who are at risk for developing type two diabetes in the near future, following up with them and providing preventive care, “we can make an impact on their development of type two diabetes.”

“We have to think about physiology,” Dr. Valent said. “How do lipids, adiponectin, leptin, and other things influence women who have gestational diabetes? Should it change our glucose-centric focus on how we treat women with diabetes to a more broad, individualized health care program?”

In summary, the two-step approach was designed to detect women at high risk for the development of type two diabetes, she said. “If we consider the women diagnosed with gestational diabetes, those are women who have the potential for developing type two diabetes. If we intervene now, that is called primary prevention.”

Thinking about the fetus, “which is the part that I love about my job because I get to think about two people,” she said, “then I have primary preventive capacity for that fetus if I can help improve the overall health condition of the mother.”

Treating GDM improves perinatal outcomes. But a screening test is supposed to be followed up on, and the challenge is that only 40 percent of women diagnosed with GDM return after delivery for a GTT. Whether they follow up with their primary care physicians is unknown. “We have a huge potential to be able to make an impact on these women if we can follow them a little more closely,” Dr. Valent said.

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