MASTER CLASS

The Consequences of GDM

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The thresholds for deciding when to begin treating hyperglycemia were established almost 50 years ago at a time when we had significantly less knowledge about the risk factors for and consequences of hyperglycemia in pregnancy. Because of this lack of understanding about the causes and consequences of hyperglycemia and our sometimes rigid adherence to these cutoffs, many women were not treated who should have been.

There is a growing recognition in the research and clinical communities that gestational diabetes mellitus (GDM) is a much more serious condition than had been previously believed even a decade ago. We now know that GDM, if not properly diagnosed and managed, can have intergenerational consequences in terms of propagating risks for obesity, diabetes, heart disease, and other disorders. Furthermore, there is a new and growing realization that even mild hyperglycemia significantly below what has traditionally been defined as diabetes can have significant adverse consequences for both mother and infant.

Perhaps the most significant complication of maternal hyperglycemia faced by ob.gyns. is the growing number of large-for-gestational-age (LGA) infants being born. For obvious reasons, LGA infants are more difficult to deliver and significantly more prone to experiencing shoulder dystocia and other injuries during normal or cesarean delivery, and cesarean delivery has its own set of complications for both baby and mother.

The large, multicenter Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study recently documented that by managing hyperglycemia – even among women who previously had not been considered to have any glucose control problems – the incidence of LGA-related problems and other adverse birth outcomes could be significantly reduced.

To discuss in detail the findings of the HAPO study and its potential clinical implications, we have invited Dr. Thomas R. Moore, professor and chairman of the department of reproductive medicine at the University of California, San Diego, to write this Master Class.

Dr. Moore's essay discusses both the unique design and findings of the HAPO study, and also explores the quandary faced by members of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in their attempts to translate HAPO's findings into clinically useful recommendations and guidelines.

In a sign of how complex and time consuming it can be to translate clinical research findings into clinical practice, the recommendations of the IADPSG are now being debated among research and medical societies, with some suggesting that the thresholds introduced by the HAPO study and advanced by the IADPSG are not significantly different from the current levels.

We greatly appreciate Dr. Moore's insights into these complicated but exciting developments. His Master Class installment will help all of us to better understand this complex issue so that we can potentially play a role in speeding up the process of changing the way we manage GDM.

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A Sea Change in the Understanding of GDM Management

The tide has turned in our understanding of both the effects of maternal hyperglycemia and the effectiveness of current treatment approaches. Consequently, we are facing an impending sea change in the way in which gestational diabetes is diagnosed and managed.

THOMAS R. MOORE, M.D.

Recent research has detailed the risks posed to a fetus exposed to hyperglycemia during pregnancy – even at levels that in the past have been considered mild and, thus, largely inconsequential. We also now have evidence that we can offer therapies for gestational diabetes mellitus (GDM) with confidence that we can use them to change the outcome for the fetus, the newborn, the child, and possibly the adult.

This impending change comes after decades of diagnosing gestational diabetes based largely on relatively arbitrary thresholds. Dr. John B. O'Sullivan and statistician Claire Mahan developed the diagnostic criteria more than 40 years ago based on certain statistical phenomena associated with the development of adult-onset diabetes after pregnancy. Before then, during the 1940s, 1950s, and 1960s, 1%-2% of all pregnant women were diagnosed with GDM.

In recent years, many of us have had the experience as clinicians of delivering larger, more obese babies whose mothers had been found to have "normal" blood glucose levels. Many of us also have delivered babies with significant adiposity, sometimes perilously low blood glucose, shoulder dystocia, nerve injuries, and other complications that typically occur as a consequence of fetal overgrowth.

We often attribute these complications to a diagnostic method we have known for some time wasn't perfect, but until recently, we did not have the clinical research findings to guide us in our efforts to fine-tune the diagnosis of GDM and turn the tide.

Insights on Fetal Risk

The landmark Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, led by Dr. Boyd E. Metzger, was an attempt to clarify what level of maternal glucose intolerance is associated with an excess risk of an adverse pregnancy outcome.

The HAPO study, which involved 15 centers in nine countries, examined the outcomes of more than 25,000 pregnancies. In designing the HAPO study, Dr. Metzger and his colleagues did something that had never formally been done before: They administered a 75-g oral glucose tolerance test (OGTT) to the mothers between 24 and 32 weeks' gestation (as close to 28 weeks as possible), and defined GDM as an abnormal 2-hour 75-g OGTT result. They then followed the births of women identified as having GDM, and compared them with the births of mothers who did not have gestational diabetes as defined by traditional measures.

Outside the United States, the 75-g, one-step OGTT has been the standard for GDM diagnosis for some time. In the United States, many of us still use an awkward two-step system in which women initially are given a 50-g oral challenge. Only if they register an excessive value on the 50-g challenge do they come back for a definitive 3-hour, 100-g OGTT.

'Among the most striking findings was that a significant number of fat babies were born to women whose blood glucose levels were considered "normal."'

Quite a few outcomes were measured in the HAPO study, but the major outcomes were birth weight greater than the 90th percentile, the level of cord-blood serum-C-peptide (an index of fetal beta-cell function and fetal hyperinsulinemia) above the 90th percentile, and percent body fat greater than the 90th percentile.

The glucose results of the majority of women remained blinded (data were not blinded if the 2-hour plasma glucose level was greater than 200 mg/dL, or diagnostic of diabetes, or if the fasting plasma glucose level exceeded 105 mg/dL or the random plasma glucose level was 160 mg/dL). After birth and the assessment of fetal outcomes, these outcomes were arrayed against earlier results of the mothers' 2-hour 75-g glucose challenge tests and the fasting blood glucose levels, both of which were measured at the same time during pregnancy. (Fasting plasma glucose levels varied from as little as 75 mg/dL all the way up to the predefined threshold of 100 mg/dL.)

Considering percent of body fat greater than the 90th percentile, one would expect no more than 10% of babies without diagnosed GDM in the mothers to have hyperinsulinemia and large amounts of body fat.

Dr. Metzger found otherwise: 17% of babies whose mothers had a fasting blood glucose of 90 mg/dL, for instance – a level most clinicians have viewed as normal – had large levels of body fat, and many of these babies also had hyperinsulinemia. Overall, there was no "golden" level of maternal glucose that predicted a fat baby. However, neonatal adiposity increased progressively as fasting blood glucose levels rose above 80 mg/dL.

In the case of 1-hour 75-g OGTT results, fatness increased progressively at levels greater than 105 mg/dL, and with 2-hour results, fatness rose progressively at levels over 90 mg/dL (Diabetes 2009;58:453-9).

Such continuous linear relationships between maternal glucose and adverse fetal outcomes were seen studywide for birth weight and other outcomes (N. Engl. J. Med. 2008;358:1991-2002).

Among the most striking findings was that a significant number of fat babies were born to women whose blood glucose levels were considered "normal."

The question at this point became, What should we do about it? Should we allow these obese babies to be born without any intervention, or can we treat them before birth?

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Insights on Treatment

Many experts have been doubtful that treatment of mothers with GDM would be effective in altering newborn outcomes. However, the Australian Carbohydrate Intolerance Study in Pregnant Women, published in 2005, concluded that early treatment of GDM reduces serious perinatal morbidity and may improve health-related quality of life. In this study, women with GDM were randomized to receive dietary advice, blood glucose monitoring, and insulin therapy as needed (the treatment group), or routine care (N. Engl. J. Med. 2005;352:2477-86).

In another randomized study published several years later, Dr. Mark B. Landon and his colleagues finally convinced many experts of the value of aggressive screening and early intervention for GDM. Dr. Landon focused on a subset of women who had an abnormal result on a 3-hour 100-g OGTT but a fasting glucose level below 95 mg/L. These women thus had only mild glucose intolerance. (An abnormal result was defined as two or three timed glucose measurements that exceeded certain thresholds: 1-hour, 180 mg/dL; 2-hour, 155 mg/dL; and 3-hour, 140 mg/dL.)

Although the ADA has revised its recommendations for diagnosis of GDM to embrace the criteria of IADPSG, neither body has issued a directive or a formal set of guidelines for clinicians.

In 14 centers across the United States, 958 patients were randomized to receive treatment of their diabetes or nothing but usual prenatal care. Treatment included formal nutritional counseling and diet therapy, along with insulin if needed. The majority of the women (93%) needed only dietary counseling and education about blood glucose control, while the other 7% needed insulin as well.

Women receiving dietary counseling checked their blood glucose levels before they got up in the morning, and 2 hours after each major meal. In essence, they planned and adjusted their diet based on their blood glucose readings.

What did we learn from this trial? We learned that the incidence of large-for-gestational-age births (greater than the 90th percentile) was cut in half from approximately 14% in the untreated group to 7% in the treated group. There also was a 10%-14% reduction in fat mass in the babies born to the women who received treatment, as well as significant reductions in mean birth weight and birth weight greater than 4,000 g. Most importantly, treatment also reduced the number of injuries that occurred during birth, while the number of small-for-gestational-age infants did not increase (N. Engl. J. Med. 2009;361:1339-48).

With these two randomized studies demonstrating significantly reduced risks with early GDM treatment, the question shifted from the broader issue of whether it is worthwhile to treat women with GDM to the more specific question of who needs treatment the most.

A New Approach

Today, in most demographic and ethnic groups in the United States, the incidence of gestational diabetes is between 4% and 12%, with a national incidence of about 8%. These are the patients we are already treating.

The HAPO trial, however, has shown us that there are a significant number of babies whose mothers have mild hyperglycemia and who are not being treated for this condition. These babies have neonatal adiposity and subsequently are being injured during the birth process.

In addition, we now have multiple epidemiologic studies demonstrating that adiposity at birth markedly increases – by as much as 30%-40% – the risk of being fat as a child and as an adolescent. Studies also have shown that the risk of developing childhood and adolescent type 2 diabetes proportionately increases with increasing neonatal adiposity.

Thus, the goal is no longer just to prevent neonatal adiposity so that babies will not be injured during birth; it now includes helping mothers control their glucose profiles so that their babies will have better health during their childhood and adult years.

However, the answer to the current, pressing question of whether we should offer treatment to women who are not now defined as having gestational diabetes is not yet clearly answered.

In 2008, after the initial release of HAPO study findings, a group called the International Association of Diabetes and Pregnancy Study Groups (IADPSG) was created to discuss the definition of gestational diabetes in light of the new HAPO findings and other research demonstrating improved outcomes with treatment.

In 2010, the consensus group released revised recommendations for glucose tolerance testing, suggesting that everyone convert to the 2-hour 75-g OGTT and that we lower the cutoff points used for diagnosis to protect as many babies as possible from becoming obese.

The group deliberated how much risk to address, or cover, with new cut points. Is a 150% increase in risk, for example, too much? Or a doubling of newborn fatness? In looking at a possible lifetime of obesity, type 2 diabetes, and heart disease, how much testing and treatment is just right? In the end, the group chose cutoff points for the fasting, 1-hour, and 2-hour plasma glucose measurements that conveyed an odds ratio for adverse outcomes of at least 1.75.

This means that a fasting plasma glucose of 92 mg/dL or more almost doubles the adverse fetal outcome risk; so does a 1-hour value after the 75-g OGTT of at least 180 mg/dL, and a 2-hour value of at least 153 mg/dL. If any one of these values is elevated, according to the IADPSG, a fetus is at risk and the mother should be treated for hyperglycemia (Diabetes Care 2010;33:676-82).

The Near Future

With the new criteria proposed by the IADPSG, the number of women who will be defined as having GDM using the 75-g OGTT will double to approximately 16%, compared with about 8% today. This doubling of incidence obviously will require additional resources and intervention.

The question now is, Are we going to adopt these new criteria? The practice approach for GDM in the United States normally follows guidelines for diabetes put forth by the American Diabetes Association and/or guidelines for pregnancy developed by the American College of Obstetricians and Gynecologists. Although the ADA has revised its recommendations for diagnosis of GDM to embrace the criteria of IADPSG, neither body has issued a directive or a formal set of guidelines for clinicians.

The National Institute of Child Health and Human Development is planning a workshop on GDM for next year, and it is quite possible that the proceedings from this NICHD workshop will inform future statements or guidelines from these organizations. In all likelihood, new screening criteria will be widely adopted within several years.

In the meantime, providers must decide what to do. There is nothing wrong with continuing two-stage testing. However, those who do should realistically consider its disadvantages: For one, this process identifies only 80%-90% of the women who actually have abnormal glucose levels, so many at-risk newborns will be missed even though their mothers were tested.

Secondly, the timing of the two-step process is problematic. Most women are given lab orders for the OGTT at about 28 weeks' gestation. By 29 or 30 weeks, they'll have results. If abnormal, the office staff must call and tell the patient to schedule the second OGTT test. Our own studies have shown that each step takes about 7-12 days to complete. In our system, it can then take up to 10 days for a woman diagnosed with GDM to receive care. She will be instructed in glucose monitoring and her care team will check with her every week.

In the end, it may be 6-8 weeks after initial testing before the woman's glucose intolerance is effectively addressed. The maximal time of fetal fat accretion is at about 34 weeks. If we do not have a diagnosis made and treatment plan underway by 32 weeks, we will have significantly decreased our chance of preventing obesity in her newborn.

Aggressive efforts to get screening done at about 26 weeks would be worthwhile, especially if you are working within a system that can accommodate a greater number of women with identified glucose intolerance. To ensure the outcomes that we're seeking, we must ensure that our patients receive adequate dietary and other interventions.

There also are questions about whether the identification of more women at risk of an adverse pregnancy outcome could itself create risk, particularly since it is well documented that women with GDM are more likely to be delivered earlier or through cesarean section, regardless of the level of achieved glucose control. (In the Landon study, interestingly, the rate of cesarean delivery was reduced in the intervention group.)

On the other hand, wider identification offers such hope for reducing fetal adiposity, and its many adverse consequences, that it should be immediately considered. ■

Dr. Moore said he had no relevant financial disclosures.

'Old' (Current) vs. 'New' (Upcoming)

Two-Step Approach to GDM Dx:

► Initial screening with a 50-g glucose challenge test at 24-28 weeks' gestation in women at greater than low risk of GDM. Women at very high risk should be screened as soon as possible after confirmation of pregnancy.

► Diagnostic 100-g oral glucose tolerance test (on separate day, after overnight fast) in women who meet or exceed chosen threshold on 50-g screening (140 mg/dL or more, or 130 mg/dL or more for higher sensitivity).

► GDM diagnosis made if at least two of these plasma glucose values are met or exceeded after the 100-g OGTT: fasting, 95 mg/dL; 1 hour, 180 mg/dL; 2 hour, 155 mg/dL; 3 hour, 140 mg/dL (if a 3-hour test is done).

One-Step Approach to GDM Dx:

► Screening of all women at 24-28 weeks' gestation not known to have type 2 diabetes with 75-g oral glucose tolerance test (after overnight fast).

► GDM diagnosis made if any one of these fasting plasma glucose values are met or exceeded: fasting, 92 mg/dL; 1 hour, 180 mg/dL; 2 hour, 153 mg/dL.

Sources: American Diabetes Association's Standards of Medical Care in Diabetes 2010 (Diabetes Care 2010;33:S11-61); American College of Obstetricians and Gynecologists Practice Bulletin, September 2001; ADA's Standards of Medical Care in Diabetes 2011 (Diabetes Care 2011;34:S11-61).