GDM and the Developing Fetus

A growing body of research has convincingly demonstrated that even periods of mild hyperglycemia during pregnancy can have long-term adverse consequences on the developing fetus. Therefore, there is a growing sentiment in the ob.gyn. and diabetes communities for an aggressive approach to the detection, treatment, and monitoring of the most frequent causes of hyperglycemic events during pregnancy. Significant controversies remain on how best to implement this approach.

In the area of gestational diabetes mellitus (GDM) treatment, multiple controversies exist regarding whether to manage GDM very aggressively (i.e., with insulin as the first line of therapy) or with less aggressive approaches first, followed by insulin as a last resort. The former approach, while likely to be effective in controlling hyperglycemia, is viewed by many physicians and their patients as not acceptable given that GDM is a relatively mild form of diabetes and most cases will resolve spontaneously after pregnancy.

In this month’s Master Class, Dr. Thomas R. Moore, professor and chairman of the department of reproductive medicine at the University of California, San Diego, returns to provide us with a superbly written essay on the state of the evidence in managing GDM. The growing prevalence of GDM in the United States and worldwide, as well as the scientific evidence linking intrauterine hyperglycemia with adverse pregnancy outcomes, has then provided a detailed analysis of the best available science on trials of dietary approaches to GDM as well as trials on oral antihyperglycemic drugs and how they compare with one another and with insulin.

Dr. Moore also demonstrates how this knowledge is being applied to his own patients as well as how they’ve been able to adapt, accept, and comply with this relatively new approach to managing GDM. Once again, we are honored that Dr. Moore has agreed to serve as the Master Class guest professor, providing important insights into how GDM might be managed optimally.

Key Points

- Prenatal exposure to hyperglycemia programs the fetus for a higher risk of becoming obese in adolescence as a result of the differing intrauterine environments (Diabetes 2000;99:2208-11).
- This and other studies have given us a body of supplementary science showing that exposure to high blood glucose in utero causes accumulation of fat in the fetus. Even though that baby fat might be lost in early childhood, prenatal exposure nevertheless genetically programs the fetus for a higher risk of developing fatness as an adult.
- As I detailed in the last Master Class in obstetrics (Ob.Gyn News, July 2011, pp. 24-25), we now also have evidence from two randomized controlled trials that interventions to control blood glucose are effective in reducing rates of newborn obesity and therefore should improve adrenal and adult health downstream.
- The two randomized trials—the Australian Carbohydrate Intolerance Study in Pregnant Women (N. Engl. J. Med. 2005;352:2477-86) and a study published several years later by Dr. Mark B. Landon and his colleagues (N. Engl. J. Med. 2009;361:1339-48)—demonstrated the positive impact of treating even mild forms of GDM, with the largest effects being on reducing newborn obesity. Although the offspring of mothers who were treated and not treated in those studies have not yet been followed into adulthood, it seems fair to expect that the children of mothers who were treated for GDM will have significantly better health profiles downstream.
- Treating GDM, and learning how to maximize glucose control, has thus proved to center stage in obstetric practice.

Trials of Dietary Change

In Dr. Landon’s landmark study, more than 90% of the women randomized to the treatment group (diet alone or diet plus nutritional (practical) care) needed only dietary counseling and education about blood glucose control for effective treatment of abnormal blood glucose levels. Surprisingly, fewer than 10% needed insulin as well.

That we can manage many of our patients with diet alone is welcome good news. To be successful with this approach, however, we must be vigilant in monitoring the effectiveness of dietary counseling and identifying early on those patients for whom dietary treatment is not enough.

We also must be more vigilant in detecting GDM, because the maximal time of fetal fat accretion is at about 32-34 weeks’ gestation. GDM is typically diagnosed at about 28 weeks’ gestation, and patients usually are not engaged in a regime of blood sugar testing and dietary change until about 30-31 weeks. If we wait until 34-35 weeks’ gestation to change course with treatment—adding insulin or oral antihyperglycemic agents—significant body fat accumulation by the fetus already will have occurred.

Screening for GDM even earlier than currently recommended, at 20 weeks’ gestation, if possible, and providing dietary counseling as early as possible are worthwhile goals. Our advice is that patients be moved on to a medication regimen if more than one-third of their blood glucose measurements are still abnormal after 2 weeks of dietary change. A more stringent standard may be more prudent, but for now we believe there is enough evidence to warrant this modest change in practice, and we find that it is a rule that most patients can understand.

We also must caution that the effectiveness of dietary change may be significantly less in many populations than it was in Dr. Landon’s study because his study focused on a subset of women who had only mild glucose intolerance. In our patient population, for example, we can achieve good glucose control with diet alone in about 60%-70% of cases.

The Science on Glyburide

Pharmacologic therapy for patients in whom dietary measures fail is no longer limited to insulin. Insulin is certainly still an option as a first-line therapy, and it is necessary as an adjunct therapy in patients who are not achieving glucose targets with another agent. It has proven efficacy and well-studied pharmacokinetics. It does not cross the placenta, and research has continued on following page

Optimal Management of Gestational Diabetes Mellitus

We now know that gestational diabetes mellitus is a serious condition that, if not properly diagnosed and managed, can have cyclic, intergenerational consequences. Newborns exposed to maternal hyperglycemia during pregnancy have a high risk of being born overweight and of eventually becoming obese children and adults. These newborns also are at a high risk of developing diabetes themselves later in life.

The prevalence of gestational diabetes mellitus (GDM) is increasing in every ethnic group. In the Kaiser Permanente system in Colorado, a state which has traditionally had the lowest obesity rate of any state in the United States, the prevalence of GDM doubled from 1994 to 2002, with significant increases in all racial/ethnic groups (Diabetes Care 2005;28:579-84). Such increases in GDM prevalence are happening worldwide—one part of a worldwide epidemic of obesity and diabetes that is outpacing our youth.

We’ve learned that GDM is one signpost on the way to the development of overt type 2 diabetes. Indeed, a majority of women with GDM will acquire diabetes within 5 years.

In the last decade or so, our clinical research focus has centered on the in utero risks to the fetus. In a striking study of the potential impact of intrauterine hyperglycemia exposure on later development, Dr. D. Dabelea and coinvestigators compared siblings in the Pima Indian population who were born before and after their mothers were diagnosed with diabetes. The children who were born after their mothers had developed diabetes had almost double the rate of obesity as adolescents than their siblings who were born before their mother’s diagnosis of diabetes. Even though these siblings ate the same diet and came from the same gene pools (with the same fathers), they experienced dramatically different health outcomes.
Glyburide dosing in Dr. Langer’s trial was increased weekly, as needed, to a maximum of 20 mg per day; women took the drug twice a day. Insulin was administered per a standard intensified schedule of six to eight hourly and regular TID (lasting 2-4 hours). Despite the impressive findings from the trial, some have contended that the results of one randomized trial are insufficient for adopting glyburide as a first-line therapy. However, several retrospective and case-controlled studies also have since shown glyburide to be a clinically effective alternative to insulin therapy, with no adverse neonatal or fetal effects. These studies have shown, moreover, that it can be easier to avoid hypoglycemia and achieve optimal glycemic control with glyburide than with insulin. One of the best large retrospective studies looked at 584 women at Kaiser Permanente Northern California and found that glyburide was at least as effective as insulin in achieving glycemic control and resulted in similar birth weights in women with GDM who had failed diet therapy alone (Am. J. Obstet. Gynecol. 2005; 193:118-24).

Several recent reviews of glyburide studies, such as one that looked at nine glyburide studies covering 745 patients taking glyburide and 645 patients taking insulin, also have been published (Ann. Pharmacother. 2008;42:483-90). In 2007, moreover, the 5th International Workshop-Conference on GDM concluded that glyburide is a legitimate alternative to insulin for GDM (Diabetes Care 2007; 30:S251-60). We also now know that unlike other, first-generation sulfonylureas that cross to the placenta freely, glyburide is 99.8% protein-bound and thus crosses the placenta only minimally.

Theoretically, there is one potential problem with glyburide. Because the drug acts by stimulating maternal pancreatic insulin production, it should essentially mimic “pancreatic burnout,” thus shortening the time to development of overt diabetes in women whose pancreas is prone to “burnout.” However, whereas 4% of the glyburide group in Dr. Langer’s trial had to eventually add insulin (and up to 10%-20% in other studies), no one in Dr. Langer’s group had to add supplementary insulin, which in this case was metformin. These women have significant insulin resistance, at the tissue level.

As ob.gyns, our experience with metformin, the other oral anti-hyperglycemic agent now available for treating GDM, came originally from its use as an infertility treatment in women with polycystic ovary syndrome (PCOS). Metformin is frequently prescribed for women with PCOS to improve ovulation. These women have significant insulin resistance and are at high risk for developing diabetes during their pregnancies. The main concern in this population, however, has been infertility, and studies have shown that metformin induces ovulation in women with PCOS. Although metformin crosses the placenta, numerous studies have shown no increase in birth anomalies in women who conceived while taking the agent. A study published a decade ago in women who chose whether or not to continue metformin treatment throughout their pregnancies showed that of those who discontinued metformin 6-10 weeks after development of GDM, compared with only 3% of those who continued their metformin treatment (Fertil. Steril. 2002;77:520-5). These results helped fuel the idea that the agent may be a logical treatment for women with GDM.

Metformin also has a theoretical advantage over glyburide since its mechanism of action gets directly to the root of the problem of GDM. Metformin is an insulin sensitizer, and the root cause of GDM is resistance to insulin, or insulin insensitivity, at the tissue level. In a study by Dr. J.A. Rowan published in 2008 that randomized more than 700 patients to either insulin or metformin, there were no appreciable differences in neonatal and maternal outcomes – from birth weight and neonatal morbidity to maternal hypoglycemia and glycemic control (N. Engl J. Med. 2008;358:2003-15). However, whereas 4% of the glyburide group in Dr. Langer’s trial had to eventually add insulin (and up to 10%-20% in other studies), no one in Dr. Langer’s group had to add insulin during their pregnancies. These women have significant insulin resistance, at the tissue level. As ob.gyns, our experience with metformin, the other oral anti-hyperglycemic agent now available for treating GDM, came originally from its use as an infertility treatment in women with polycystic ovary syndrome (PCOS). Metformin is frequently prescribed for women with PCOS to improve ovulation. These women have significant insulin resistance and are at high risk for developing diabetes during their pregnancies. The main concern in this population, however, has been infertility, and studies have shown that metformin induces ovulation in women with PCOS. Although metformin crosses the placenta, numerous studies have shown no increase in birth anomalies in women who conceived while taking the agent. A study published a decade ago in women who chose whether or not to continue metformin treatment throughout their pregnancies showed that of those who discontinued metformin 6-10 weeks after development of GDM, compared with only 3% of those who continued their metformin treatment (Fertil. Steril. 2002;77:520-5). These results helped fuel the idea that the agent may be a logical treatment for women with GDM.

Indeed, the downside to metformin, this and other studies have shown, is a high so-called failure rate – the need for supplementary insulin, which in this case typically occurs later in the pregnancy – of between 30% and 50%. On the other hand, patients generally will be more satisfied starting treatment with metformin than insulin. In weighing glyburide and metformin, patients should be counseled about the chances of their needing insulin later in the pregnancy: about 10% with glyburide and closer to 50% with metformin.

In terms of glycemic control and other outcomes, several smaller, recent studies comparing the two agents have shown no differences between them. Interestingly, most studies have shown less maternal weight gain in patients taking metformin than glyburide – about 6 pounds – but the significance of this difference is unclear since the basal and peak blood glucose weights were not appreciably different.

Dr. Moore said he had no relevant financial disclosures.