MASTER CLASS

GDM and the Developing Fetus

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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. Dr. Moore's Master Class briefly discusses the growing prevalence of GDM in the United States and worldwide, as well as the scientific evidence linking intrauterine hyperglycemia with adverse pregnancy outcomes. He then provides 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 serve as the Master Class guest professor, providing important insights into how GDM might be managed optimally. ■

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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.

THOMAS R. MOORE, M.D.

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 overtaking our youth.

We've learned that GDM is one sign post 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 in adolescence as a result of the differing intrauterine environments (Diabetes 2000;49:2208-11).

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 (see 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 adolescent 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 moved 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 (versus usual prenatal 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 hypoglycemic agents – significant body fat accumulation by the fetus already will have occurred.

Screening for GDM even earlier than currently recommended, at 26 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 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

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Key Points

► Prenatal exposure to hyperglycemia programs the fetus for a higher risk of being born overweight, of becoming obese in adolescence or adulthood, and of developing diabetes later in life. Two randomized trials have demonstrated the positive impact of treating even mild forms of GDM.

► Many patients can be managed with diet alone, but the effectiveness of dietary treatment must be carefully monitored, with insulin or oral antihyperglycemic agents added early – before significant body fat is accumulated by the fetus.

► Glyburide is just as effective as insulin in achieving optimal glycemic control and is significantly less likely to cause hypoglycemia in mothers, with no adverse neonatal or fetal effects, numerous studies have shown. Glyburide is not a 12-hour medication in pregnant women as it is in nonpregnant women, however. Ob.gyns must appreciate the dosing implications of the agent's different pharmacodynamics in pregnancy.

► Metformin also has equivalent efficacy to insulin, and several small recent studies have shown no significant difference with glyburide. Metformin has a theoretical advantage over glyburide in that it's an insulin sensitizer, but the downside is a higher chance of needing supplementary insulin later in pregnancy. Patients can be counseled accordingly.

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shown that it may be beneficial by "resting" pancreatic islet cells.

Insulin is not an optimal therapy for GDM for several reasons, however. Many patients find it cumbersome to use, and most offices are not equipped for, or used to, teaching women how to give themselves the insulin injections. Insulin itself is also unfamiliar to many patients and can even be scary; some of the families we care for see insulin as a stigma, believing that a person who takes insulin has diabetes while a person who takes a pill does not truly have the condition.

In our practice, we have found that women who take oral hypoglycemics are more likely to have better glycemic control, probably because their drug compliance is better. With insulin, our patients tend to be suboptimally compliant.

Glyburide, one of the oral anti-hyperglycemic drugs that we have been able to transfer from use in the nonpregnant diabetic population to use during pregnancy, has been well used and studied by this point in time.

When Dr. Oded Langer and his colleagues led the first and only randomized trial comparing glyburide and insulin more than a decade ago, women with GDM were rarely treated with a sulfonylurea drug largely because of reports of prolonged severe hypoglycemia in neonates born to mothers who were receiving the drug at the time of delivery. There were also questions about whether glyburide, a second-generation sulfonylurea, could effectively control postprandial peaks in blood glucose while avoiding periods of hypoglycemia in the mother.

In the nonpregnant population, glyburide has been used for decades as a twice-daily oral medication. After months of use, patients develop active metabolites that prolong the drug's half-life and enable it to last for 12 hours, at least.

Glyburide use in pregnancy is a slightly different story, however. Patients take the medication for a relatively short time and consequently may not build up the active metabolites that nonpregnant patients acquire. The metabolic changes in pregnancy also make women vulnerable to hypoglycemia at certain times of the day, typically in the late morning, the late afternoon, and between 3 a.m. and 4 a.m.

Dr. Langer's trial, which randomized 404 women with GDM to receive glyburide or insulin, demonstrated similar outcomes in the insulin and glyburide groups. There were no differences in mean birth weight, the percentage of large for gestational age newborns, macrosomia, fetal anomalies, or newborn hypoglycemia. The rate of maternal hypoglycemia, however, was much higher in the insulin-treated group; 20% of the women receiving insulin experienced symptomatic hypoglycemia, compared with only 2% of the women taking glyburide.

In short, glyburide was just as effective as insulin in achieving desired levels of glycemic control (a fasting blood glucose less than 90 mg/dL and 2-hour postprandial glucose of 120 mg/dL) and controlling fetal obesity, while being significantly less likely to cause hypoglycemia in the mothers. (N. Engl. J. Med. 2000;343:1134-8).

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 regular NPH (intermediate-acting, lasting 6-12 hours) 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, numerous retrospective or 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 tend to cross 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 could potentially promote "pancreatic burnout," thus shortening the time to development of overt diabetes in women whose pancreas is struggling to begin with. Women who are obese and have significant insulin resistance at the start of their pregnancies thus might be susceptible to pancreatic burnout. Although this potential effect has not been demonstrated in any trials, it must be kept in mind.

It would be informative to conduct long-term follow-up studies that track the children of mothers who used glyburide during their pregnancies, but at this point it is unclear if such studies will be designed and carried out. The likelihood of additional randomized trials being conducted is practically nil, given the extent to which women already are choosing the oral hypoglycemics over insulin.

Glyburide in Practice

As clinicians, we must appreciate that the pharmacodynamics of glyburide are quite different in pregnant women, with important dosing implications for our patients. Indeed, for pregnant women, glyburide is not the 12-hour medication that it is in nonpregnant women.

During pregnancy, glyburide action peaks about 2.5 hours after it's taken, and the increased renal clearance and metabolism of pregnancy (in addition to the short duration of therapy in this patient population) leave the drug with a "useful" life of only about 6-8 hours.

Because blood glucose peaks 60-90 minutes after a meal, we instruct our patients to take a glyburide dose a full hour before a planned meal. Otherwise, postprandial glucose peaks will not be controlled. Usually, a dose taken an hour before breakfast will help control postprandial peaks after breakfast and lunch but will not last for dinner. Another dose 1 hour before an evening meal can be given.

To effectively control fasting blood glucose, we instruct patients to take a glyburide dose between 10 p.m. and midnight so that the drug will still be active in the early morning when it is needed. If the dose is taken too early at night – at 8-9 p.m., for instance – it will peak between 10 p.m. and midnight, and will not be working at 6 a.m.

As it is with insulin, careful glucose monitoring is critical for determining optimal administration of glyburide and for balancing glyburide action with meals and snacks. Individual glycemic profiles should be analyzed each week, with the goal of keeping fasting blood glucose below 90 mg/dL, and postprandial levels below 130 mg/dL, while preventing maternal hypoglycemia.

Attention must be paid not only to times of consistent elevation in blood glucose levels, but also to the potential for dosage overlap – for instance, a prelunch dosage administered to correct consistently high postprandial glucose levels after the midday meal could lead to low blood glucose levels at about 4-5 p.m. as its action overlaps with the end duration of a morning dose. Patients should always be prepared for vulnerable times and have a glucose tablet, juice box, or food with them to correct any periods of hypoglycemia.

Insulin should be added if more than 30% of blood glucose readings are above target with administration of 15-20 mg/day of glyburide.

Doses, Durations of Two Oral Antihyperglycemic Drugs

	Normal typical dose	Peak	Half-life	Effective duration
Glyburide	1.25-7.5 mg twice daily	2.75 hours	2.8 hours	6-10 hours
Metformin	500-1,000 mg twice daily	2.0 hours	4.3 hours	12 hours

Sources: Clin. Pharmacol. Ther. 2009;85:607-14; Drug Metab. Dispos. 2010;38:833-40.

Metformin as an Option

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 GDM 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 conceive 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, 31% developed 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), 47% of the patients taking metformin in this trial had to add insulin to maintain glycemic control.

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 their chances of 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 statistical difference 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 babies' birth weights were not appreciably different. ■

Dr. Moore said he had no relevant financial disclosures.