MASTER CLASS

Treating Gestational Diabetes

BY E. ALBERT REECE, M.D., PH.D., M.B.A.

Within our society there are several conditions that are currently demanding a significant amount of our attention. Among them are obesity and diabetes.

In certain populations—in ethnic minority groups and among Native Americans in particular—there has clearly been a rise in gestational diabetes. There is also an association between the increased incidence of diabetes in pregnancy and an increasingly obese population. The two problems, we are learning, are truly entwined.

In the Master Class published in September, we addressed the diabetes pandemic, which some refer to as "diabesity" because of its association with obesity, and how diabetes complicates pregnancy for the mother and threatens fetal development and outcome.

Sometimes diabetes during pregnancy is of the type 2 variety. Gestational diabetes and type 2 diabetes are sometimes confused in their presentation and hence their diagnosis, however. Admittedly, a precise diagnosis of type 2 diabetes is often made in retrospect following the conclusion of the pregnancy. The diagnostic distinction is important, however, as a diagnosis of type 2 diabetes often drives a more serious approach to glycemic control.

In light of the increasing incidence of diabetes in pregnancy, the age-old problem of optimum treatment takes on even more significance.

Diet is still a mainstay. Insulin therapy remains difficult for patients to accept because it requires injections on a daily basis. Oral agents have been avoided for years because of concerns about safety and the lack of well-controlled data to establish whether such agents cross the placenta and may be potentially harmful to the fetus.

We are now at a juncture in our therapeutic maturity, however, where an increasing amount of information and data are available on the use of therapeutic options such as oral antidiabetic agents.

In light of this crossroads—the convergence of significantly more knowledge and a significantly higher prevalence of diabetes—we thought it high time to review the subject of gestational diabetes, and particularly the contemporary therapeutic options that are now available and can be applied in pregnancy.

I have again invited Oded Langer, M.D., Ph.D., who in September discussed why diabetes must be detected early and treated seriously, to discuss the latest research on oral antidiabetic agents in pregnancy and provide some useful perspective on diabetes management in our patient population.

Dr. Langer is an internationally recognized expert on diabetes in pregnancy who has written and lectured extensively on this subject. He is the Babcock Professor and chairman of the department of obstetrics and gynecology at St. Luke's–Roosevelt Hospital Center, a hospital affiliated with Columbia University in New York. ■

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Oral Antihyperglycemic Agents and Diabetes in Pregnancy

It is well recognized that the complications and adverse perinatal outcomes associated with gestational diabetes and type 2 diabetes in pregnancy are glucose dependent. The main question in medical management, therefore, is how to maximize glycemic control.

The choice of medication should be determined by the ability of the drug to achieve the targeted level of glycemic control. For some patients, oral antihyperglycemic agents will be the drug of choice while in others combination therapy and/or insulin should be used.

BY ODED LANGER, M.D., PH.D.

For years, pharmacologic therapy for diabetes in pregnancy was limited to insulin. Obstetricians feared that oral antihyperglycemic agents, as an alternative to insulin therapy, could cause adverse pregnancy outcomes, particularly congenital anomalies and metabolic complications. Because of these concerns, sulfonylurea drugs were contraindicated in pregnancy.

These recommendations were founded, however, on anecdotal reports and poorly designed retrospective studies that were performed prior to the availability of second-generation sulfonylureas such as glyburide.

Today, there is clear evidence from in vivo and in vitro studies that glyburide does not cross the placenta in any appreciable quantity while metformin, another oral glucose-lowering agent, crosses the placenta freely.

Several randomized studies (five glyburide and two metformin studies), as well as other well-designed studies published over the last decade, also have demonstrated that glyburide is as effective and safe as insulin therapy for glycemic control during pregnancy.

Research has shown, moreover, that it's the blood glucose levels—not the drugs themselves—that cause adverse outcomes.

This is good news, because the use of oral antihyperglycemic agents enhances drug compliance for the patient.

Taking a tablet once in the morning and once in the evening is easier, more convenient, and less expensive than giving oneself insulin injections several times a day. Given the choice of insulin injections versus tablets, almost all women will opt for the latter.

Offering glyburide as a safe and effective alternative to insulin has been recommended by several editorials and professional organizations. Indeed, the use of glyburide has become the standard of care in the management of gestational diabetes mellitus (GDM) in many centers and private practices throughout the United States.

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It is important to appreciate, however, that in general, as disease severity increases, there is diminishing success in achieving the desired levels of glycemic control.

Although the majority of women with gestational diabetes will benefit from the use of these drugs (approximately 80%), fewer women with type 2 diabetes will be able to achieve optimal glycemic control.

The emphasis overall in diabetes management must therefore be on the level of glycemic control achieved by the patient, with the failure of a drug signaling the need to change the drug algorithm.

Safety, Efficacy of Glyburide

Oral antihyperglycemic drugs—most commonly glyburide and metformin—are the first-line drugs for treating nonpregnant women with type 2 diabetes. These patients are typically older and suffer from greater disease severity (higher fasting and postprandial blood glucose levels and a decreased pancreatic reserve of 50%-80%). They therefore are not comparable to patients with gestational diabetes who are relatively younger and have greater pancreatic reserve.

This begs the following question: If the oral antihyperglycemic drugs are in fact safe for the fetus and can potentially optimize glycemic control—enabling patients to reach targeted levels of glucose control in pregnancy with the same efficacy as insulin—why should GDM patients who represent the milder form of intolerance on the glucose continuum not be treated with these drugs?

In the early 1990s, my colleagues and I evaluated the potential of first-generation and second-generation sulfonylureas to cross the placenta. Using the single-cotyledon placental model—a model that is widely used to characterize the transport and metabolism of drugs and nutrients—we found only minimal transport of glyburide in either the maternal-fetal or the fetal-maternal direction (Am. J. Obstet.Gynecol. 1991;165:807-12).

The transfer of glyburide remained negligible even when we varied the albumin concentration and increased maternal glyburide levels to 100 times the therapeutic level. In no case was there any appreciable metabolism of the agent. First-generation sulfonylureas, on the other hand, crossed the placenta in this model. Metformin did as well, almost freely.

Thereafter, several studies from different centers confirmed that glyburide does not cross the placenta significantly. The studies demonstrated, for instance, that 99.8% of the glyburide is bound to albumin, that the agent has a short elimination half-life, and that effluxes are affected from the fetal-maternal direction. Research also confirmed that metformin does cross the placenta.

In a later prospective, randomized trial comparing glyburide and insulin in 404 women with GDM, my colleagues and I found no significant differences in either the degree of glycemic control or perinatal outcomes (N. Engl. J. Med. 2000;343:1134-8). Target levels of glycemic control were achieved in 82% of the patients receiving glyburide and 88% of those receiving insulin.

There were no significant differences between the groups in the rate of infants who were large for gestational age or who had macrosomia, a ponderal index greater than 2.85, lung complications, hypoglycemia, or fetal anomalies.

We also tested the cord serum at delivery and found similar cord-serum insulin concentrations in the two groups. Glyburide was not detected in the cord serum above the level of 10 ng/mL.

Since 2000, more than 20 studies (4 of them randomized) have been published that show similar success rates with gly-

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buride and insulin in achieving good glycemic control in gestational diabetes as well as similar perinatal outcomes. Most of the studies have been small and not randomized. Oftentimes, however, well-designed retrospective or case-control studies can be just as reliable. In this case, the studies collectively provide a solid basis for evaluation.

In a meta-analysis published last year, investigators concluded that the studies suggest there are no increased perinatal risks with glyburide compared with insulin for the treatment of GDM (Ann. Pharmacotherapy 2008;42:483-90).

Nine studies met the inclusion criteria for the analysis, which totaled 745 glyburide-exposed pregnancies and 637 insulin-exposed pregnancies. Women were typically treated starting at 24 weeks of gestation.

Glyburide Management

1. Start with 2.5 mg in the morning. If needed, drug titration should occur every 3-7 days.
2. Increase the morning dose by 2.5 mg.
3. Add the evening dose of 5 mg.
4. Increase the morning dose by 5 mg to 10 mg.
5. Increase the evening dose by 5 mg to 10 mg.

Note: The maximal dose is 20 mg daily.

Source: Dr. Langer

The use of glyburide was not associated, the investigators said, with risk of macrosomia, differences in birth weight, rate of large-for-gestational-age births, differences in gestational age at birth, ICU admission, or risk of neonatal hypoglycemia.

Metformin as an Option

Glyburide and metformin have different mechanisms of action. Glyburide works on the pancreas to stimulate insulin secretion. Metformin, which belongs to the class of oral antihyperglycemic agents known as the biguanides, lowers glucose levels by decreasing hepatic glucose production and decreasing peripheral insulin resistance.

Some have suggested that because metformin does not stimulate insulin secretion, it is less likely than glyburide to cause hypoglycemia and may be the preferable choice for treating diabetes in pregnancy.

While we have not directly compared metformin and glyburide in this regard, our data and data from other studies demonstrate that the rate of maternal hypoglycemia is significantly higher with insulin than with glyburide therapy. In one study using continuous blood glucose measurements, we showed that the maternal rate of hypoglycemic episodes was five times higher in insulin-treated patients than in glyburide-treated patients (Obstet. Gynecol. 2004;104:88-93).

Earlier findings suggesting the opposite—that glyburide is more likely to cause hypoglycemia than is insulin therapy—were from studies in much older, nonpregnant women. Diabetes in patients who are in their 50s through their 80s cannot be compared, in general, to the less severe disease in younger women of reproductive age.

Metformin, like glyburide, has been shown in numerous studies to have no adverse effect in pregnancy in terms of anomalies. The first large randomized, controlled trial to assess the safety and efficacy of metformin versus insulin—published last year—found similar efficacy in achieving target levels of glucose control and no difference in perinatal outcomes among 751 women randomized to one of the two groups (N. Engl. J. Med. 2008;358:2003-15).

Like glyburide, metformin is a class B drug. Because metformin crosses the placenta, physicians must take this into consideration when deciding which oral antihyperglycemic agent to choose. Even if a drug crosses the placenta, however, it should not automatically be considered contraindicated for use in pregnancy because the majority of drugs used in pregnancy cross the placenta without adverse effect to the fetus.

Also of possible concern is the fact that the rate of large-for-gestational-age infants in the New England Journal of Medicine (NEJM) metformin-versus-insulin study was twice the rate of large-for-gestational-age infants in our NEJM study comparing glyburide with insulin. This suggests that the rate of success in achieving glycemic control in pregnancy may be lower with metformin than with glyburide.

We need other studies, however, that directly compare glyburide with metformin (rather than comparing each with insulin), and the resultant perinatal outcomes and glycemic control, in order to address this issue.

Metformin is a popular drug for the treatment of polycystic ovary syndrome (PCOS), which presents the question of whether patients on metformin for PCOS should conceive while on the drug, or halt the drug if they unexpectedly conceive.

The answers in these cases call for individual judgment. In my opinion, metformin is a drug that can be used in pregnancy, as long as one keeps in the back of one's mind the fact that it does cross the placenta. One must also consider that although recent retrospective and prospective trials have shown no adverse effects of metformin in terms of anomalies, no published randomized study has evaluated pregnancy outcomes when patients were treated with the drug from preconception throughout gestation.

With respect to continuing either metformin or glyburide throughout pregnancy for those patients who are treated with these drugs during the preconception stage, the main concern in my opinion is whether the drugs can achieve the levels of glycemic control desired in pregnant women with type 2 diabetes. Because current data have shown that the level of glycemia—and not the drug—is associated with any increased rate of anomalies, I believe patients can remain on these drugs as long as the targeted level of glycemic control is maintained.

Overall, considering that we have a more extensive, more conclusive body of evidence for glyburide than metformin—and considering that glyburide does not cross the placenta—metformin is generally a second choice for me.

Pearls of Management

GDM and type 2 diabetes are essentially the same disease. They are similar in risk factors and in metabolic and endocrine abnormalities. Both are characterized by peripheral insulin resistance, decreased insulin secretion (reflecting declining beta-cell function), and impaired regulation of hepatic glucose.

GDM represents an early stage of the deterioration continuum toward type 2 diabetes. It is characterized by a milder glycemic profile. As I alluded to in a previous Master Class installment ("How Type 2 Diabetes Complicates Pregnancy," September 2009, p. 28), though, it is increasingly believed that many of the women who are diagnosed with gestational diabetes actually meet the criteria for type 2 diabetes.

Because oral antihyperglycemic agents are the gold standard for therapy in type 2 in the general population—the landmark U.K. Prospective Diabetes Study (UKPDS) of type 2 diabetes showed that 70% of patients achieved desirable levels of glucose control with the use of glyburide—it is sensible to assume that women with GDM or early type 2 diabetes will respond to oral therapy with even greater success.

In general, oral glucose-lowering agents will decrease HbA_{1c} levels by 1%-2% (insulin, by 1%-2.5%). This roughly corresponds to a drop in fasting blood glucose levels of 30-60 mg/dL.

Oral therapy should be initiated when women cannot achieve fasting blood glucose levels of 95 mg/dL or less, or postprandial levels of 120 mg/dL or less after 2 hours. Diet and exercise can be recommended first for many of our patients, of course, but we must do so with careful consideration of the time that we have to meet target levels of control and prevent macrosomia and other adverse outcomes. Research has shown that at least 60% of patients with GDM eventually will require pharmacologic therapy.

Any pharmacologic therapy necessitates frequent dose adjustment to obtain the desired effect of the drug. Oral antihyperglycemic drugs should be increased only to the maximum dose allowed (20 mg daily in the case of glyburide).

The maximal dose of a drug and steady state are different in nonpregnant and pregnant patients, of course, because drug clearance is higher during pregnancy. However, in order to minimize any potential for complications like maternal hypoglycemia, our aim in diabetes management is to provide the minimal dose that will result in a desirable level of glycemic control.

Different oral antihyperglycemic agents act through diverse mechanisms, and the drugs' characteristics provide a physiological approach to the treatment of type 2 diabetes and GDM. Combination therapies will enhance the effect of these drugs on glucose metabolism, and "whole" patient care (including glucose monitoring, education, and diet adherence) will determine overall success in managing this disease and maximizing the quality of perinatal outcomes.

When insulin is added for the patient treated with oral agents, a single dose at bedtime can be sufficient in many cases. One of the benefits of this combination is the need for a lower dose of insulin. Insulin therapy alone should be used when other combinations have failed and is not limited by a maximum dose.

In obstetrics, we've lagged at least 2 decades behind the field of diabetes management in the general population. Now, however, we should be embracing the use of oral antihyperglycemic agents as the standard of care. We may find with further research that other drugs may have a greater therapeutic effect, but for now glyburide is the best frontline choice for glycemic control. ■

DR. LANGER *said he has no disclosures relevant to this article. To comment, e-mail him at obnews@elsevier.com.*

Key Points

► The level of glycemic control achieved—not the mode of therapy—is the key to improving outcomes in GDM and type 2 diabetes in pregnancy.

► Medical therapy with oral agents should be reserved for patients whose fasting plasma glucose levels remain above 95 mg/dL (or whose postprandial levels remain above 120 mg/dL) despite diet therapy and for those who are not appropriate candidates for diet therapy alone.

► The aim of therapy is to provide the minimal dose that will result in a desirable level of glycemic control and the least amount of complications for the mother.

► Well-designed studies have shown no association between oral antihyperglycemic agents and congenital malformations.

► Glyburide, metformin, and insulin are equally effective for GDM treatment at all disease severity levels.

► Glyburide is as effective as insulin for the treatment of obese GDM patients.

► Combination therapy or insulin therapy should be initiated if desired levels of glucose control are not achieved with one oral agent.

► Medication is just one component of intensive therapy. "Whole" patient care is also important.

Source: Dr. Langer