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.

Diabetes therapy and/or insulin treatment must therefore be on the level of that in general, as disease severity increases. For some patients, oral antihyperglycemic agents will be the drug of choice while in others combination therapy and/or insulin should be used.

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, sulfonfonyurea 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 sulfonfonyureas 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.

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, most all women will opt for the latter.

Oral antihyperglycemic therapy is safe and effective alternative to insulin. 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.

Safety, Efficacy of Glyburide

Oral antihyperglycemic drugs—most commonly glyburide and metformin—are the first-line drugs for treating non-pregnant 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 safer 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 or insulin concentrations in the two groups. 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.

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.
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-con- trol studies can be just as reliable. In this case, the studies collectively provide a solid basis for evaluation.

In a recent analysis published last year, investigators concluded that the studies suggest there are no increased perinatal risks with glyburide compared with insu- llin for the treatment of GDM (Ann. Pharmacotherapy 2008;42:483-90). Nine studies met the inclusion criteria for the analysis, which totaled 745 gly- buride-exposed pregnancies and 637 insulin-exposed pregnancies. Women were typically treated starting at 24 weeks of gestation.

The use of glyburide was not associ- ated, 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 se- cretion. Metformin, which belongs to the class of oral antihyperglycemic agents known as the biguanides, lowers glucose levels by decreasing hepatic glu- cose production and decreasing periph- eral 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 glu- cose measurements, we showed that the maternal rate of hypoglycemic episodes was five times higher in insulin-treated patients than in glyburide-treated pa- tients (Obstet. Gynecol. 2004;104:88-93).

Earlier findings suggesting the oppo- site—that glyburide is more likely to cause hypoglycemia than is insulin ther- apy—were from studies in much older, nonpregnant women. Diabetes in pa- tients 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 ef- ficiency of metformin versus insulin— published last year—found similar effi- cacy in achieving target levels of glucose control and no difference in perinatal outcomes among 751 women random- ized to one of the two groups (N. Engl. J. Med. 2008;358:2003-13).

Like glyburide, metformin is a class B drug on the New England Journal of Medicine (NEJM) metformin-versus-in- sulin 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 met- formin (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 unexpect- edly conceive.

The answers in these cases call for in- dividual judgment. In my opinion, met- formin is a drug that can be used in preg- nancy, as long as one keeps in the back of one’s mind that its use is to be a temporary therapy. One must also consider that although recent retrospective and prospective trials have shown no adverse effects of metformin in terms of anom- alies, no published randomized study has evaluated pregnancy outcomes with patients who were treated with the drug from preconception throughout gestation.

With respect to continuing either met- formin or glyburide throughout preg- nancy for those patients who are treat- ed with these drugs during the preconception stage, therapy should continue in my opinion whether the drugs can achieve the levels of glycemic control de- sired 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 in- creased rate of anomalies, I believe pa- tients 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 met- formin—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 essential- ly the same disease. They are similar in risk factors and in metabolic and en- docrine abnormalities. Both are charac- terized by peripheral insulin resistance, decreased insulin secretion (reflecting declining beta-cell function), and im- paired regulation of hepatic glucose.

GDM represents an early stage of the transition continuum toward type 2 diabetes. It is characterized by a hyperglycemic profile. As I alluded to in a pre- vious Master Class installment (“How Type 2 Diabetes Complicates Pregnann- cy,” September 2009, p. 28), though, it is increasingly believed that many of the processes diagnosed with gesta- tional 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 de-irable 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 HbA1c 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. One strategy should be initiated when women cannot achieve fasting blood glu- cose levels of 95 mg/dL or less, or post- prandial levels of 120 mg/dL or less af- ter 2 hours. Diet and exercise can be recommended first for many of our pa- tients, 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 40% of patients with GDM eventu- ally will require daily insulin therapy.

Any pharmacologic therapy necessi- tates frequent dose adjustment to obtain the desired effect of the drug. Oral anti- hyperglycemic 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, be- cause drug clearance is higher during pregnancy. However, in order to mini- mize any potential for complications like maternal hypoglycemia, our aim in dia- betes management is to provide the minim- al dose that will result in a desirable level of glycemic control.

Different oral antihyperglycemic agents act through diverse mechanisms, and the drugs’ character- istics and the patient’s antihyperglycemic profile will determine which oral antihyperglycemic agent to choose. Even a physiological approach to the treatment of type 2 diabetes and GDM. Combina- tion therapies will enhance the effect of these drugs on glucose metabolism, and “whole” patient care (including glucose monitoring, education, and diet adher- ence) 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 front-line 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 a desirable level of glycemic control and the least amount of complica- tions for the mother.

Source: Dr. Langer

Glyburide Management
1. Start with 2.5 mg in the morning. If needed, drug titra- tion should occur every 3-7 days.
2. Increase the morning dose by 2.5 mg to 10 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