

Oral Medications for Diabetes in Pregnancy: Use in a Rural Population

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■ **IN BRIEF** The oral agents glyburide and metformin are both recommended by many professional societies for the treatment of gestational diabetes mellitus (GDM). Both therapeutic modalities have published safety and efficacy data, but there remains much debate among experts. Providers need a clear treatment plan for GDM based on a predictable level of clinical success in obtaining treatment goals. The proper selection of ideal candidates is paramount in achieving clinical success with the use of these medications in the treatment of GDM. This article presents clinical strategies for using oral agents in the management of GDM based on a pragmatic approach taken in a group of rural Native American women.

Although variations in diagnostic guidelines and screening methods make determining the true burden of gestational diabetes mellitus (GDM) difficult, consensus exists that its occurrence is increasing with the steady rise of type 2 diabetes and obesity and advancing maternal age (1). A recent national evaluation suggested the prevalence to be as high as 9.2% (1). Even a modest degree of hyperglycemia has been associated with adverse maternal, fetal, and neonatal outcomes (2). Maternal complications of GDM include increased rates of diabetes later in life, preeclampsia, gestational hypertension, and the need for cesarean delivery; offspring are more likely to be macrosomic and to experience birth trauma, shoulder dystocia, and operative vaginal delivery (3). Hence, adequate control of hyperglycemia is imperative to optimize maternal, fetal, and neonatal outcomes. When lifestyle modification and dietary intervention fail to produce appropriate glycemic control, pharmacological therapy is indicated.

Traditionally, insulin has been the drug of choice for GDM management. However, the use of oral agents has been increasing, and the American College of Obstetrics and Gynecology supports the use of either oral or injectable medications as acceptable therapies for women with GDM (3). Approximately 6% of providers treated pregnancies with the oral agent glyburide in 2000, and that percentage rose to 64% by 2011 with emerging research and new recommendations. By 2007, glyburide became the most common form of treatment for GDM (4–6). Oral medications are attractive options for patients given their ease of administration, lower cost, comparable efficacy, and improved adherence (7).

Controversy exists in the literature regarding the use of the oral agents metformin and glyburide, and the U.S. Food and Drug Administration (FDA) has not endorsed these category B medications as appropriate therapy for women with GDM (8). Both drugs have altered pharmacokinetics during pregnancy, and both

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cross the placenta (7). Critics of the use of these agents cite concerns about the relative lack of data surrounding their safety, optimal dosage, and efficacy in comparison to the robust data regarding insulin in the management of GDM (7–10).

Glyburide is a sulfonylurea that enhances insulin secretion in peripheral tissues. Metformin is a biguanide that inhibits hepatic gluconeogenesis and stimulates glucose uptake by the peripheral tissues. Some recent observational studies, experimental studies, and meta-analyses have established oral agents as effective relative to insulin and reported no consistent data demonstrating an increase in adverse maternal, fetal, or neonatal outcomes (11). However, researchers also acknowledge the limitations of these studies to date and the lack of data on long-term maternal and neonatal effects; this void prohibits organizations from establishing concrete recommendations for the use of these agents.

Providers must communicate these issues when counseling patients regarding treatment options for GDM refractory to lifestyle interventions. Although insulin remains the mainstay of treatment for GDM based on the most robust data, there exist subsets of patients for whom oral agents may be suitable and effective alternatives, provided clinicians are willing to either abandon use of these medications in favor of insulin when glycemic control is not achieved or use a combination of these oral medications with insulin when necessary to improve glycemic control.

Clinical Application

Given that controversy exists regarding how best to manage the treatment of women with GDM, data from successful clinical programs often can assist in the decision-making process. The following sections of this article share our practical approach for such clinical decision-making but should not be considered to be extrapolated from statistically significant data

nor always consistent with prevailing guidelines from major professional societies. Our GDM management program, located in a rural setting, serves more than 300 women per year who have some form of diabetes in pregnancy. The program is in its tenth year, and more than 90% of the babies from these pregnancies are born at a weight appropriate for gestational age. Our patients often present with unique social, geographic, and financial barriers that hamper access to resources such as high-quality foods and exacerbate food insecurity. They typically have cultural practices governing food choices that do not fit within the recommended dietary prescriptions and traditional guidelines of recognized and highly regarded professional societies. However, our patients with GDM still have successful clinical outcomes.

The primary factor associated with successful GDM management in our patient population is patient empowerment. When patients are told that they failed a glucose tolerance test, often the only portion of the message they hear is that they have simply “failed.” That message does not set the necessary tone for building patients’ self-confidence in their ability to control their disease for the duration of their pregnancy. We provide reassurance in teachable moments and establish a nurturing learning environment. Although achieving euglycemia is the primary goal in GDM care, providers must simultaneously protect each woman’s birth story. Poor diabetes control should not be the main thing she remembers about her pregnancy. Enabling her to take control of her blood glucose allows for GDM to be considered only a small part of her pregnancy experience rather than an overwhelming stressor centered on failure and fear.

Providers have many tools available for the treatment of GDM. Medical nutrition therapy (MNT) is the cornerstone of initial GDM therapy (12). Many women can

manage their glucose with thoughtful meal planning, provided there are no barriers to following the detailed recommendations. These barriers, including depressed socioeconomic status, exist among our patients, and providers often revisit the inability to overcome such obstacles, furthering the concept of failure. Empowering patients newly diagnosed with GDM should focus on the positive self-care behaviors they are able to achieve, such as remembering to check blood glucose levels or completing a meal diary.

If MNT is not successful, the rapid application of another intervention is necessary. No consensus exists regarding the threshold at which medications should be started in GDM management (13). The decision-making process we have used has yielded successful outcomes for our population for many years. We use the Sweet Success Clinical Guidelines for Care as our program framework (14). We consider adequate glycemic control to be 80% of fasting and postprandial values in the target range. We use a fasting blood glucose (FBG) goal of 60–89 mg/dL and a 1-hour post-meal target of 100–129 mg/dL.

Glyburide

Oral diabetes agents can be used successfully in pregnancy. About 25% of our patients with GDM use glyburide successfully to manage their blood glucose during pregnancy. All providers who care for the women with GDM should be able to determine ideal candidates for this medication (10). FBG, weeks of gestation, and weight gain to date are the three main data points we consider when deciding whether glyburide may be a successful option for a given patient. Because glyburide is a secretagogue, its success is dependent on the patient having a healthy and functioning pancreas that can respond well to the drug. If a patient’s FBG is significantly elevated, providers should suspect that she may not have the physiological capacity to secrete the

elevated amount of insulin required during pregnancy, and glyburide is unlikely to correct this problem (15). Glyburide also potentiates weight gain, so it is important to assess total weight gain to date and consider how long the patient may need to use glyburide (16). Recommendations in the literature state that glyburide can be used predictably when FBG is <110 mg/dL after 25 weeks' gestation (12). We are more conservative in our patient selection, using glyburide for patients with an FBG \leq 100 mg/dL in the third trimester who have not exceeded the recommended weight gain for their BMI based on the Institute of Medicine's guidelines.

After 1 week of data gathering, if a patient's FBG is above target but <100 mg/dL despite MNT, we typically start glyburide 2.5 mg at bedtime. If the postmeal glucose values are slightly above target but not severely elevated to >200 mg/dL, we also would add an equivalent morning dose. We continue to discuss and encourage physical activity and MNT so the patient can bring the effects of all three components to bear on her glycemic management. We download glucose meters and evaluate meal diaries weekly, in person or remotely, titrating medication dosages accordingly to reach and maintain an 80% glycemic control rating. We titrate until the maximum glyburide dose of 20 mg/day is reached. If control is suboptimal at the maximum dose, the patient is switched to insulin.

The literature describes the failure rate of glyburide to achieve euglycemia to be in the range of 15–40% (13). We experience a much lower rate of 6% in our population, and we attribute this to the fact our cohort has a much lower starting FBG value than is typical in relevant research studies. Additionally, our glyburide cohort has experienced no significant adverse neonatal outcomes; we have had no documented admissions to the inpatient pediatric department for neonatal hypoglycemic episodes. However, our overall cohort on gly-

buride is relatively small, and these outcomes are not sufficiently powered to be statistically significant.

Metformin

Metformin was originally derived from an herbal folk remedy using the French lilac plant and was found in 1929 to lower blood glucose in rabbits. It did not become available in Europe until 1958 and did not receive FDA approval for type 2 diabetes treatment until 1994. Pregnancy is associated with a state of markedly increased insulin resistance (14). Metformin decreases insulin resistance. Metformin has been shown to be comparable to insulin in achieving glycemic control in pregnancy (7). It can be used in the treatment of GDM as monotherapy or in conjunction with insulin. Metformin is associated with less maternal weight gain and hypoglycemia than glyburide (12). It has been shown to have a failure rate of 10–46% in achieving glycemic control in pregnant women with diabetes (7).

Choosing candidates for metformin treatment of GDM involves many of the same evaluations and considerations as for glyburide. Maternal side effects of metformin, including nausea, vomiting, and diarrhea, are common (10). Adding a medication with this particular set of side effects to a pregnancy state can be problematic from the standpoint of patient satisfaction and may limit adherence to the care plan. Side effects often can be diminished by starting women on a low-dose regimen of 500 mg twice daily for the first week of therapy and then titrating doses to an effect based on blood glucose data as therapy continues.

In our cohort, metformin has not been tolerated as well as glyburide because of its gastrointestinal side effects. We tend not to use metformin as a first-line oral glycemic agent or as monotherapy because most patients are diagnosed with GDM in the third trimester of pregnancy, and optimal glycemic control must be

achieved and maintained relatively quickly. Instead, we view metformin as a useful tool for patients with a high degree of insulin resistance. For our GDM patients who are on high doses of insulin with frequent titrations, we often add metformin to improve insulin sensitivity. For example, we have patients with mealtime doses of a fast-acting analog insulin approaching 80–100 units, with matching basal insulin doses. Such patients typically also have a BMI in the obese or severely obese range. We see significant improvement in insulin effect with the addition of metformin within 1–2 weeks in these patients, and this mirrors the experience reported elsewhere (12,17).

Conclusion

Glyburide and metformin have been endorsed as viable treatment options for GDM. Clinicians need to have a clear understanding of selection criteria for appropriate candidates for these treatment options. Because debate continues about the best use of these agents in GDM management, real-life successes of high-volume programs that achieve positive outcomes with these agents can serve as examples that can be extrapolated to other programs and clinics.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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