From Research to Practice / Diabetes and Pregnancy

Oral Antidiabetic Drugs in Pregnancy: The Other Alternative

In the United States, depending on the diagnosis criteria used, 135,000–200,000 women annually develop gestational diabetes mellitus (GDM), adding to the number of pregnant women who already have either type 1 or type 2 diabetes. There has also been a significant increase (~33%) in the incidence of type 2 diabetes with its presumed parallel risk for obesity in addition to the development of adolescent obesity in the offspring of diabetic women.1

Two main factors have contributed to the dramatic increase in pharmacological therapy: recognition that GDM is an early stage in the development of type 2 diabetes and increased awareness of the impact of the metabolic syndrome on public health and its appearance in 20–50% of women who have had GDM. This article outlines the management approach (intensified treatment) and describes the use of oral antidiabetic agents (mainly glyburide) to prevent glycemic extremes (i.e., hypoglycemia and hyperglycemia) in pregnant women with GDM and type 2 diabetes.

Fundamental Structure of Intensified Therapy
Intensified therapy is an approach to achieving established levels of glycemic control. Two breakthrough studies in nonpregnant diabetic patients demonstrated the effectiveness of intensified therapy: the Diabetes Control and Complications Trial3,4 in type 1 diabetes and the U.K. Prospective Diabetes Study in type 2 diabetes.5 Regardless of the type of diabetes, the intensified approach incorporates several components:

In Brief
The use of oral antidiabetic drugs in pregnancy is an accepted treatment modality for women with gestational diabetes mellitus (GDM). This efficacious option provides physicians more choices that, in turn, translate into more complex decision making for the management of GDM. However, regardless of the mode of therapy, whole patient care (glucose monitoring, education, diet adherence, and so forth) will determine overall success in managing this disease and the potential to maximize the quality of perinatal outcome.
Goals of Pharmacological Treatment

Targeted levels of glycemic control achieved with intensified therapy prevent microvascular and macrovascular complications in nonpregnant diabetic patients. However, the thresholds for targeted levels of glycemic control are higher than those used for the definition of normoglycemia in nondiabetic pregnant women. Thus, one must distinguish between normoglycemic levels and the thresholds recommended to optimize outcome in pregnant and nonpregnant diabetic women.

Regardless of the treatment modality, the primary goal is always to attain the recommended level of glycemic control, thereby reducing hyperglycemic extremes (i.e., incidence of hypoglycemia, hyperglycemia, and ketosis) while maximizing perinatal outcome. In pregnancy, the criteria used for targeted levels of glycemic control at our institution are:

- Mean blood glucose: 90–105 mg/dl
- Fasting blood glucose: 60–90 mg/dl
- Preprandial blood glucose: 80–95 mg/dl
- 2-hour postprandial blood glucose: < 115 mg/dl

How do you know when diet has failed and pharmacological therapy should be initiated? There is no consensus and there are no hard data to guide this decision. Authoritative organizations differ on the threshold of severity that necessitates pharmacological intervention with glubyrde or insulin. Some suggest as a threshold a fasting plasma glucose of ≥ 95 mg/dl, which will decrease the rate of macrosomic and large-for-gestational-age (LGA) infants, whereas others suggest ≥ 105 mg/dl.

All authorities agree that drug therapy should be initiated when 2-hour postprandial glucose levels are ≥ 120 mg/dl or 1-hour levels are ≥ 140 mg/dl. Using these standards, 30–50% of women with GDM require pharmacological therapy when diet alone fails to reduce glycemic levels.

In a study evaluating the time required to achieve glycemic control with diet alone during a 4-week period, 70% of patients with a fasting plasma glucose < 95 mg/dl achieved established levels of glycemic control within 2 weeks with no substantial improvement thereafter. Furthermore, the rate of LGA infants was similar regardless of treatment modality (diet or insulin). In contrast, in patients with a fasting plasma glucose > 95 mg/dl, the majority of patients failed to achieve the desired level of glycemic control throughout the 4-week period, with a resulting threefold higher rate of LGA infants in diet-treated patients. Thus, it is reasonable and appropriate to recommend that patients with a fasting plasma glucose > 95 mg/dl be assigned to pharmacological therapy, especially considering the high rate of obesity in patients with GDM.

Patients with a fasting plasma glucose < 95 mg/dl may be candidates for a trial of diet therapy for a 2- to 3-week period before initiation of pharmacological therapy. However, it should be noted that ~ 30% will fail to achieve the desired levels of glycemic control and will require pharmacological therapy. The failure to introduce pharmacological therapy in a timely fashion may lead to fetal hyperinsulinemia, which is central to the pathophysiology of diabetes complications in pregnancy. These complications include an increase in neonatal intensive care unit admission; metabolic, hematological, and respiratory complications; increased rate of accelerated fetal growth; maternal and birth trauma; cesarean delivery; and risk for stillbirth. In addition, there is an increased rate of congenital malformations in the infants of type 1 and type 2 diabetic women. Conversely, premature initiation of pharmacological therapy in women who could have achieved glycemic control with diet alone leads to unnecessary drug treatment. When GDM is diagnosed after 30–33 weeks' gestation and there is limited time available to influence the desired level of control, pharmacological intervention is recommended. There is greater flexibility when GDM is diagnosed early in the third trimester.

Oral Antidiabetic Agents

Different oral hypoglycemic and anti-hyperglycemic agents have diverse mechanisms of action to correct or improve the pathological lesion responsible for glucose intolerance. Therefore, these drugs provide an enhanced approach to the treatment of type 2 diabetes and GDM. Furthermore, combination therapies will further improve the effect of these drugs on glucose metabolism. Insulin therapy, in contrast to therapy with oral agents, is designed to mimic the physiological...
secretion of endogenous insulin.

Oral agents are a pragmatic alternative to insulin therapy in pregnancy because they are easy to administer and noninvasive and therefore user-friendly. Since the original study in 2000, many experts and authoritative organizations in the United States (e.g., the Fifth International Workshop on Gestational Diabetes and the North American Diabetes in Pregnancy Study Group) have endorsed the use of glyburide (a sulfonylurea) as an alternative pharmacological therapy to insulin during pregnancy.

The introduction of any new drug in pregnancy will raise concerns about fetal and maternal safety. The ultimate proof that a drug cannot affect the fetus during pregnancy is founded on its inability to cross the placenta. The majority of drugs used in pregnancy cross the placenta. Thus, even if a new drug crosses the placenta, it remains to be proven that it will cause a teratogenic effect on the fetus in utero. If there is no adverse effect on the fetus, the drug can be used.

Glyburide does not cross the placenta. Our original observations have been reconfirmed by several studies. Glyburide has been safely used in pregnancy without adverse effects on the fetus. In contrast, metformin, rosiglitazone, and pioglitazone freely cross the placenta. We await further evidence on safety when fetuses are exposed to these drugs. In the case of metformin with patients who have polycystic ovary syndrome, data from retrospective studies give us hope for its safe use. The ongoing Metformin in Gestational Diabetes study from Australia and New Zealand is evaluating in a randomized design the efficacy of metformin versus insulin use. Because there is no clinical study to date reporting on the use of thiazolidinediones in pregnancy, these agents should not be prescribed.

**Attributes of Glyburide**

Glyburide is the most common oral agent used in GDM and is wholeheartedly endorsed by authoritative organizations. The drug increases insulin secretion and diminishes insulin resistance by lowering glucose toxicity. Its onset of action is ~ 4 hours, and its duration of action is ~ 10 hours. Thus, after achieving the targeted therapeutic level, glyburide covers the basal requirement as well as postprandial glucose excursions.

The starting dose is 2.5 mg orally in the morning. If the targeted level of glycemia is not attained, add 2.5 mg to the morning dose. If indicated (after 3–7 days), add 5 mg in the evening. Thereafter, increase the dose in 5-mg increments to a maximum of 20 mg/day. If the patient does not achieve targeted levels of glycemic control, add long-acting insulin to the regimen or assign the patient to insulin therapy alone (Figure 1).

In our first randomized study in 2000, we enrolled 440 women between 11 and 33 weeks’ gestation with singleton pregnancies who had GDM requiring treatment (failed oral glucose tolerance test and fasting plasma glucose level of 95–140 mg/dl). Patients were randomly assigned to receive either glyburide (n = 201; initial dose 2.5 mg orally, increasing by 5 mg to a total of 20 mg) or insulin (n = 203; initial dose 0.7 units/kg subcutaneously 3 times/daily, increasing each week as necessary) for glycemic control. Subjects were required to measure their glucose values seven times daily.

Blood glucose profile characteristics before and at the conclusion of therapy were comparable for the two groups. Eighty-two percent of the glyburide- and 88% of the insulin-treated subjects were able to achieve targeted levels of glycemia. However, eight glyburide-treated women (4%) failed to achieve the desired level of control early in the third trimester and were transferred to insulin therapy. None of the patients developed severe symptoms of hypoglycemia. However, in the insulin-treated group, a significantly higher rate of subjects had 1–6% of their SMBG results in the hypoglycemic range (< 40 mg/dl).

The glyburide- and insulin-treated groups had similar rates of preeclampsia.

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**Figure 1. Decision tree for pharmacological treatment of GDM.**

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**GDM or type 2 diabetes**

Postprandial blood glucose levels of 120–180 mg/dl or fasting blood glucose of 95–140 mg/dl

**Dose and adjustment**
1. 2.5 mg, morning
2. Increase by 2.5 mg first week
3. Add 5 mg, evening
4. Increase morning 5 mg
5. Increase evening 5 mg

**Maximum:** 20 mg/day

**Glyburide**

**Combination therapy**

**Insulin**

2.3 dose in the morning
1/3 dose in the evening

**Morning 1:2 ratio**
Short:Intermediate

**Evening 1:1 ratio**
Supper regular: Bedtime intermediate
As we used continuous glucose monitoring and found comparable pregnancy outcomes with either glyburide or insulin therapy.

Several retrospective and randomized studies have evaluated the efficacy of oral agents during pregnancy, with an 80–85% reported success rate in studies using glyburide treatment. Moreover, when insulin and glyburide were compared, similar success rates were reported and were comparable to insulin in glycemic control and pregnancy outcome.

We further analyzed the association between glyburide dose, GDM severity, and selected maternal and neonatal factors. We found that glyburide dose increased with GDM severity. The success rate (i.e., achievement of glycemic control) decreased as disease severity increased. However, there was no difference between glyburide- and insulin-treated patients at each level of severity. Thus, achieving glycemic control—not the mode of pharmacological therapy—is the key to improving pregnancy outcome in GDM. When costs of insulin therapy and glyburide treatment are compared, the latter is considerably less expensive.

The Road Ahead
In the future, more pharmacological alternatives will become available. These may include metformin and other oral antidiabetic drugs, insulin glargine, oral insulin, and a technologically improved insulin pump that can interact directly with blood glucose levels. Different oral hypoglycemic agents have different mechanisms of action. A detailed discussion of the seven classes of oral agents is beyond the scope of this review but can be found elsewhere.

Insulin therapy involves daily injections, which may lead to suboptimal adherence by many women. In many developing countries, women cannot afford insulin therapy. Our studies and others have demonstrated that both diet- and insulin-treated women have comparable psychological profiles in different ethnic groups. However, it is self-evident that given the choice of insulin injection versus tablets, patients will invariably prefer taking two tablets daily instead of at least three daily injections.

Sulfonylureas are the only oral agent group studied in women with GDM in randomized controlled trials. However, other oral hypoglycemic agents may have an even greater therapeutic effect in controlling abnormal levels of glycemia. Although the evidence suggests that glyburide is as effective as insulin in maintaining desired glycemic levels and results in comparable outcomes, it should be noted that achievement of both glucose and outcome goals is conditional on the overall successful management of women with GDM.

The use of glyburide should be based on evidence-based criteria. The two randomized studies and the ~20 retrospective studies provide a sound base for evaluation. To be considered Level I in the U.S. Preventive Service Task Force criteria for quality, evidence needs to be the result of a single properly designed, randomized, controlled trial. Clinical experts have consistently applauded and welcomed the results of the glyburide study as convincing data that glyburide is a safe and effective alternative therapy for use in women with GDM. The existing body of research should encourage us to rely on evidence-based knowledge and not emotion-based misinformation when considering this medication for use with diabetic pregnant women.

References


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