Use of Oral Hypoglycemic and Insulin Agents in Pregnant Patients

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KEYWORDS
- Insulin • Pregnancy • Glyburide • Metformin • Gestational diabetes
- Type 1 and type 2 diabetes

KEY POINTS
- Diabetes mellitus (DM) complicates 6% to 7% of all pregnancies in the United States, and 85% of the cases are caused by gestational diabetes.
- During pregnancy, women with type 1 DM require insulin because of their lack of insulin production, whereas women with type 2 DM are often transitioned from an oral hypoglycemic agent to insulin.
- The management of diabetes using insulin depends on a combination of short- and long-acting insulin.
- The goals of plasma glucose control during pregnancy are a fasting sugar of 60 to 95 mg/dL and 2-hour postmeal sugar of 120 mg/dL or less.
- Current studies indicate that the insulin analogue glargine (Lantus) is a safe and effective treatment of pregnant patients with diabetes.
- Oral hypoglycemic agents (glyburide, metformin) can be alternative medications to treat gestational DM. However, a larger percent of women using metformin (46.3%) compared with glyburide (4.0%) may need supplemental insulin for good control.

INTRODUCTION

Diabetes mellitus (DM) is a condition that results in elevated blood glucose levels. DM occurring outside of pregnancy has been classified as either type 1 or type 2.

- Type 1 DM results from the lack of production of insulin by the pancreas.
  - Accounts for 5% to 10% of patients diagnosed with diabetes in the general population¹
Type 2 DM results from the body’s resistance to the effects of insulin.
  - Accounts for 90% to 95% of all patients with diabetes and most women of reproductive age with diabetes

Gestational DM (GDM) is a complication of pregnancy characterized by carbohydrate intolerance diagnosed during pregnancy. As the rates of obesity and sedentary lifestyle increase among women in the United States, so do the rates of GDM, now affecting approximately 5% of all pregnancies. It has been estimated that DM complicates approximately 6% to 7% of all pregnancies in the United States, and 85% of those cases are caused by GDM.2

The treatment of diabetes in pregnancy starts with proper nutritional counseling and dietary intervention as well as a reasonable exercise program. Pregnant women with type 1 DM will require insulin therapy throughout their pregnancy because of their lack of insulin production. Women with type 2 DM are often transitioned from an oral hypoglycemic to insulin once their pregnancy is confirmed. Women diagnosed with GDM are initially treated with diet modification. Those patients with GDM who do not attain adequate glycemic control have traditionally been treated with insulin during pregnancy; however, over the past decade, based on results from various trials indicating the efficacy and safety of oral hypoglycemic medications (glyburide and metformin) are increasingly used for treatment of GDM.3–9

With proper treatment, the goals of plasma glucose levels in pregnancy are

- Fasting 60 to 95 mg/dL
- Two hours after meals 120 mg/dL or less

This review focuses on the use of insulin and oral hypoglycemic medications for the treatment of diabetes in pregnancy.

INSULIN

During the late nineteenth century, several scientists discovered the function of the pancreas: an organ that produced a substance that could regulate blood glucose as well as digestive enzymes. This substance was a peptide hormone and came to be known as insulin, the major signal regulating carbohydrate metabolism. It is produced by the B cell of the pancreas, secreted into the hepatic portal circulation, and acts by both (1) inhibiting hepatic gluconeogenesis and glycolysis and (2) stimulating glucose uptake in the liver, muscle, and fat.

During that era, diabetes in pregnancy was a known entity, which often led to rapid premature death because no treatment was available. It was Drs Frederick Banting and Charles Best who, in the early 1920s, extracted a substance from animal pancreas that eventually became well known as insulin. The treatment of humans with diabetes with this extract was a success, and the discovery led to the Nobel Prize in 1923. Although not a cure for diabetes, the commercial availability of insulin remains one of the most important discoveries in medicine.10

Before the use of insulin in pregnant women with diabetes, rates of perinatal morbidity and mortality were extraordinarily high.11 Even until the mid 1940s, the perinatal mortality rate in the United States and Europe stood at 40%. Following subspecialty care for these patients, the perinatal morbidity and mortality sharply decreased over the next several decades.12 This decline was in large part caused by the improvement in blood sugar control with the use of insulin. In addition, the widespread use of home glucose monitoring using portable monitors has allowed the management of gestational diabetes to shift from an inpatient to an outpatient setting.
TYPES OF INSULIN

The management of diabetes using insulin depends on a combination of short- and long-acting insulin. See Table 1 for a summary of the various types of insulin and their characteristics. Rapid-acting insulin types include insulin lispro (Humalog) and insulin aspart (Novolog) and are used just before mealtime to help quickly reduce blood sugar. Their onset of action is on the order of a few minutes, and their biologic activity peaks within 1 to 3 hours. These types are usually used in combination with intermediate-acting insulin, NPH and Lente, and long-acting agents, such as Ultralente and insulin glargine (Lantus).

In addition to the agents mentioned earlier, there are several premixed combinations of insulin supplying a mixture of short- and long-acting agents in one injection, which are available either in bottle or insulin pen form. The combinations of insulin are available in various percentages depending on patient need. In general, they are given twice daily before mealtime.

TREATMENT OF DM IN PREGNANCY WITH INSULIN

Experience with insulin in pregnancy was historically confined to those patients with type 1 diabetes. Nowadays, it is common for pregnant patients with type 1 DM to control blood sugars with the assistance of a continuous subcutaneous insulin pump along with continuous blood sugar monitoring.13

As the incidence of type 2 DM and GDM has increased along with the average body mass index of pregnant women, the need for insulin to attain glycemic control in GDM has also increased. Since their introduction, insulin analogues are the preferred choice for the treatment of pregnant women with diabetes because of their superior pharmacologic profiles, leading to greater flexibility and convenience of dosing. But is there a benefit to treating patients with GDM, especially if only short-term? There have been several studies examining the efficacy of injectable insulin in GDM. Treating patients with GDM has been shown in various trials to reduce the risk of shoulder dystocia and macrosomia.14 In addition, the Australian Carbohydrate Intolerance Study in Pregnant Women demonstrated a reduction in the rate of composite serious perinatal complications, including perinatal death, shoulder dystocia, nerve palsy, or birth trauma (adjusted relative risk [RR] 0.33; 95% confidence interval [CI] 0.14–0.75).15

Over the past few years, clinical experience with insulin analogues in pregnancy has increased. Relatively recent data support the use of longer-acting agents, such as insulin glargine, both in patients with pregestational and gestational diabetes. Before

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Generic</th>
<th>Brand Name</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td>Lispro</td>
<td>Humalog</td>
<td>15–30 min</td>
<td>30–90 min</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td>Aspart</td>
<td>Novolog</td>
<td>10–20 min</td>
<td>40–50 min</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
<td>Apidra</td>
<td>20–30 min</td>
<td>30–90 min</td>
<td>1.0–2.5</td>
</tr>
<tr>
<td>Short acting</td>
<td>Regular (R) Insulin pump</td>
<td>Humulin novolin Velosulin</td>
<td>30–60 min</td>
<td>2–5 h</td>
<td>5–8</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td>—</td>
<td>NPH (N)</td>
<td>1–2 h</td>
<td>4–12 h</td>
<td>18–24</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>Lente (L)</td>
<td>1.0–2.5 h</td>
<td>3–10 h</td>
<td>18–24</td>
</tr>
<tr>
<td>Long acting</td>
<td>—</td>
<td>Ultralente</td>
<td>30 min to 3 h</td>
<td>10–20 h</td>
<td>20–36</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>Lantus</td>
<td>1.0–1.5 h</td>
<td>No peak</td>
<td>20–24</td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
<td>Levemir</td>
<td>1–2 h</td>
<td>6–8 h</td>
<td>Up to 24</td>
</tr>
</tbody>
</table>

Table 1
Various types of injectable insulin
2009, there had been limited published experience with insulin glargine in pregnancy. Fang and colleagues\textsuperscript{16} reported the results of 52 pregnant women receiving insulin glargine and compared them with a similar cohort of patients managed with NPH insulin. Both patients with pregestational and gestational diabetes were included in both groups. In this study, the investigators found no increased maternal or neonatal morbidity associated with the use of insulin glargine. Among patients with pregestational diabetes, there was a lower rate of macrosomia (relative risk [RR], 0.38; 95% confidence intervals [CI], 0.17–0.87), neonatal hypoglycemia (0% treated with glargine and 25% treated with NPH), and neonatal hyperbilirubinemia (RR, 0.27; 95% CI, 0.07–0.98) in the cohort taking insulin glargine when compared with NPH.

An observational study by Negrato and colleagues\textsuperscript{17} in 2010 showed similar efficacy and safety of insulin glargine in pregnancy among both patients with pregestational and gestational diabetes, with decreased adverse outcomes when compared with patients with diabetes using NPH. The long-acting nature of insulin glargine accompanied by minimal peak activity makes it an ideal choice to maintain steady-state blood glucose control during pregnancy.\textsuperscript{18} The hesitation in the widespread use of insulin analogues is likely caused by the limited data on safety in pregnancy. Although further research with larger numbers is warranted, the aforementioned studies suggest that insulin glargine is a safe and effective insulin analogue that may be considered in the treatment of pregnant patients with diabetes.

Although insulin has been the gold standard in the treatment of patients with diabetes in pregnancy, there are risks associated with its use:

- Allergic reactions
- Injection-site reactions
- Hypoglycemia

These risks, along with the issues of dissatisfaction among patients in having to take injections, noncompliance, and difficulty with monitoring and adjusting the insulin dosage, have made the use of oral hypoglycemics a more attractive option to pregnant patients.

**ORAL HYPOGLYCEMIC MEDICATIONS**

In the past, oral hypoglycemic agents were contraindicated in pregnancy because of concerns regarding fetal teratogenicity and the concern that these medications (primarily first-generation sulfonylurea agents) may cause fetal hyperinsulinemia resulting in increased rates of macrosomia (because insulin is a growth factor) and neonatal hypoglycemia.\textsuperscript{19} Currently, women with pregestational diabetes (type 2 DM) who start pregnancy being treated with oral hypoglycemic medications are usually switched to insulin because of the lack of studies demonstrating the safety and efficacy of these medications in early pregnancy.\textsuperscript{20}

Most pregnant women are screened for gestational diabetes during the second trimester (24–28 weeks). The pathophysiology of GDM is caused by insulin resistance and also the insufficient secretion of insulin by the pancreas.\textsuperscript{21} Therefore, oral hypoglycemic agents that may improve insulin sensitivity or insulin secretion are logical treatment options for GDM.

Over the past decade, several studies have found that either glyburide (a second-generation sulfonylurea) or metformin (a biguanide) may be used as alternative therapeutic options for the treatment of GDM during pregnancy.\textsuperscript{3–9} Because the treatment of GDM is initiated in the second trimester well after organogenesis, the concern for teratogenicity is minimal when used for the treatment of GDM. Compared with insulin, oral hypoglycemic medications
Because glyburide and metformin are the 2 oral hypoglycemic medications that have been prospectively studied for the treatment of GDM, this review focuses on these 2 medications.

**GLYBURIDE**

Glyburide acts by enhancing the release of insulin from the pancreas. It is metabolized by the liver. Glyburide is the most well-studied oral hypoglycemic medication for the treatment of GDM and is the most common oral hypoglycemic medication used to treat GDM by obstetricians. The initial starting dosage of glyburide is 2.5 mg once or twice a day, with a maximum dosage of 20 mg/d.22 It is available in 1.25-mg, 2.5-mg, and 5.0-mg tablets. Glyburide is associated with a much lower rate of hypoglycemia (1%–5%) as compared with insulin (71%).22

The placental transport of glyburide from mother to fetus studied using an ex vivo technique is much less (3.9%) when compared with first-generation sulfonylurea drugs, such as tolbutamide (21.5%) and chlorpropamide (11.0%).23 These findings suggest that fetal exposure to maternally administered glyburide may be low or insignificant. Further evidence to support the minimal passage of glyburide across the placenta was seen in a randomized trial whereby glyburide was not detected in the cord serum of any infant whose mother had been treated with glyburide during pregnancy.3

In a randomized trial comparing glyburide with insulin in the treatment of GDM conducted by Langer and colleagues,3 no significant differences were noted in the daily blood glucose concentrations and glycosylated hemoglobin values between women who were treated with glyburide versus insulin. There were also no significant differences between the two groups in the rates of macrosomia, large-for-gestational-age infants, lung complications, hypoglycemia, admission to the neonatal intensive care unit, and fetal anomalies.3 About 4% of the women treated with glyburide did not obtain adequate glycemic control and had to be switched to insulin. A recent meta-analysis examining randomized trials comparing glyburide with insulin in the treatment of GDM found no substantial difference in maternal or neonatal outcomes.5 Based on the results of these studies, glyburide may be considered an alternative medication for the treatment of GDM. Patients should be made aware that certain women may not achieve adequate glycemic control using glyburide and will, therefore, require insulin for treatment.

**METFORMIN**

Metformin acts primarily by suppressing glucose production by the liver. It also increases insulin sensitivity, enhances peripheral glucose uptake, and decreases the absorption of glucose from the gastrointestinal tract. The usual starting dosage is 500 to 850 mg/d, which can be increased to a maximum dosage of 2500 mg/d. It is available in 500-mg, 850-mg, and 1000-mg tablets. The most common adverse effects of metformin are the following:

- Common side effects
  - Gastrointestinal upset, including
    - Diarrhea
    - Cramps
    - Nausea
Vomiting
- Increased flatulence
- Serious potential side effect
  - Lactic acidosis
  - Very rare
  - Most of these cases seem related to comorbid conditions (eg, impaired liver or kidney function)

Metformin is considered a first-line drug of choice for the treatment of type 2 diabetes. In ex vivo placental perfusion studies, metformin was noted to cross the placenta with a maternal-to-fetal transfer rate of 10% to 16%. Therefore, an intriguing question is whether or not women with type 2 diabetes who are treated with metformin should continue taking this medication during the preconception period and throughout their pregnancy. There have been limited reports regarding the use of metformin in the treatment of type 2 diabetes from the preconception period through pregnancy. In studies published by Coetzee and Jackson, 22 women treated with metformin were compared with 42 women who were treated with insulin. There were no differences in the perinatal mortality rate between the two groups. There were no cases of maternal hypoglycemia or lactic acidosis. Metformin use in the first trimester was not associated with an increased risk of congenital anomalies.

The use of metformin in the first trimester of pregnancy during the time of organogenesis has also been examined in women with polycystic ovarian syndrome. These women were treated with metformin to improve fertility. In an observational trial of 72 women who conceived using 2.5 g/d of metformin, there were no cases of lactic acidosis, fetal anomalies, or maternal or neonatal hypoglycemia. In a follow-up study, at 18 months, the infants whose mothers were exposed to metformin during the first trimester showed no differences in height, weight, or motor and social skills when compared with matched controls.

In the largest randomized controlled trial comparing metformin with insulin in the treatment of GDM, Rowan and colleagues randomized 733 women (363 received metformin and 370 received insulin) at between 20 and 33 weeks. They found that neonatal complications (neonatal hypoglycemia, rates of respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar scores <7, and preterm birth <37 weeks) were not increased in the women treated with metformin as compared with insulin (RR, 1.00; 95% CI, 0.90–1.10). It is important to note that in this study, 46.3% of the women taking metformin required supplemental insulin at some point in their pregnancy to obtain adequate glycemic control. This study also found that women preferred metformin over insulin treatment.

Based on the limited number of studies regarding the long-term effects of in utero exposure, the use of metformin for the treatment of diabetes in pregnancy is limited and is often individualized depending on the patient’s circumstances. Similar to glyburide, women who are treated with metformin in pregnancy should be aware that a certain number of women may not achieve adequate glycemic control with just the oral hypoglycemic medication and may need to be switched to insulin.

**SUMMARY**

Insulin remains the standard medication for the treatment of all types of patients with diabetes during pregnancy. The choice of the type of insulin to use should be individualized based on practitioner and patient preference. Glyburide and metformin may be considered as alternative medications in the treatment of GDM.
REFERENCES


