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Gestational diabetes mellitus management with oral hypoglycemic agents

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ABSTRACT

Oral hypoglycemic agents such as glyburide (second-generation sulfonylurea) and metformin (biguanide) are attractive alternatives to insulin due to lower cost, ease of administration, and better patient adherence. The majority of evidence from retrospective and prospective studies suggests comparable efficacy and safety of oral hypoglycemic agents such as glyburide and metformin as compared to insulin when used in the treatment of women with gestational diabetes mellitus (GDM). Glyburide and metformin have altered pharmacokinetics during pregnancy and both agents cross the placenta. In this article, we review the efficacy, safety, and dosage of oral hypoglycemic agents for the treatment of gestational diabetes mellitus. Additional research is needed to evaluate optimal dosage for glyburide and metformin during pregnancy. Comparative studies evaluating the effects of glyburide and metformin on long-term maternal and fetal outcomes are also needed.

Gestational diabetes mellitus (GDM) complicates 2–10% of pregnancies in the US.[1] This condition is characterized by increased insulin resistance and the inability of beta cells to compensate for the increasing degree of insulin resistance. GDM is usually diagnosed late in the second trimester (24–28 weeks of gestation). Uncontrolled GDM can contribute to serious adverse pregnancy outcomes for the mother, fetus, and neonate. GDM is associated with neonatal hypoglycemia, respiratory distress syndrome, and macrosomia,[2] as well as maternal hyperglycemia, urinary tract or other infections, hypertensive disorders of pregnancy, and polyhydramnios.[2] Some of these women will be diagnosed with type 2 diabetes postpartum, and 35–60% of women with GDM will develop type 2 diabetes mellitus over the next 10–20 years.[1]

Historically, insulin has been the drug of choice for the management of women with GDM. However, the use of oral hypoglycemic agents as alternatives to insulin for the treatment of GDM during pregnancy has been increasing. The comparable efficacy, lower cost, ease of administration, and better patient adherence to oral hypoglycemic agents compared to insulin makes oral therapy attractive.[3–6] The most

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extensively studied oral hypoglycemic agents in pregnancy are glyburide (second-generation sulfonylurea) and metformin (biguanide). Although efficacy of oral agents in the treatment of women with GDM is quite good, failure to achieve glycemic control still occurs in ~20% of women, which creates an opportunity for further optimization of therapy.[3] In this review, we discuss the use of oral hypoglycemic agents focusing on glyburide and metformin for the treatment of women with GDM.

Oral hypoglycemic medications

Glyburide

Glyburide is a second-generation sulfonylurea that works primarily by enhancing insulin secretion. Glyburide is FDA approved for the treatment of patients with type 2 diabetes mellitus.[7] Early use of first-generation sulfonylureas such as chlorpropamide[8] and tolbutamide[9] resulted in concerns regarding teratogenicity, neonatal hypoglycemia, and fetal hyperinsulinemia, thus limiting their use during pregnancy. Maternal hyperglycemia, as well as moderate to high placental transfer and the prolonged fetal/neonatal half-life of the first-generation sulfonylureas, is the likely cause of these adverse events.[8,9] Both chlorpropamide and tolbutamide have been found to have similar umbilical cord and maternal blood concentrations.[10]

Several randomized controlled studies have compared glyburide to insulin for the treatment of GDM.[3,4,11,12] Glyburide was shown to be comparable to insulin in controlling maternal glucose and decreasing the incidence of macrosomia.[4] Langer et al.[3] ($n = 404$) reported that 82% of the subjects achieved glycemic control (self-monitored fasting glucose $\leq$95 mg/dL) with glyburide ($n = 165$) compared to 88% with insulin ($n = 179$). In a later study, the authors compared efficacy of glyburide and insulin for treatment of women with GDM, stratified for severity of disease (fasting plasma glucose $\leq$95 mg/dL vs $>$95 mg/dL).[4] The authors found that both glyburide and insulin were equally effective in treating GDM at both severity levels ($n = 404$).[4] A smaller randomized study that compared insulin to glyburide in Asian Indian women with GDM ($n = 23$) reported no significant differences in glycemic control (mean = 2-h postprandial glucose concentrations) between insulin and glyburide treatment.[11]

The efficacy of glyburide was also reported in prospective and retrospective cohort studies. A prospective observational study ($n = 64$) evaluating glyburide monotherapy (maximum glyburide dose 10 mg twice daily over 1 week) reported a 19% treatment failure rate (fasting blood glucose $>$90 mg/dL and 1-h postprandial glucose $>$130 mg/dL) with glyburide.[13] The authors reported gestational age at the time of dietary failure and mean fasting blood glucose prior to initiating glyburide to be the two most significant indicators of glyburide success. Factors favoring glycemic control with glyburide therapy were mean fasting blood glucose $\leq$110 mg/dL and mean 1-h postprandial blood sugar $\leq$140 mg/dL before 30 weeks' gestation, or not requiring medication until after 30 weeks (sensitivity 98% and specificity 65%).[13] In a retrospective study of women with GDM ($n = 75$), Conway et al.[14] found that 84% of patients receiving 2.5–20 mg/day of glyburide ($n = 63$) achieved glycemic control (overall mean glucose $\leq$105 mg/dL, fasting $\leq$95 mg/dL, and 2-h postprandial $\leq$115 mg/dL), while 16% ($n = 12$) required conversion to insulin. However, among those who could not maintain euglycemia with glyburide therapy, only two patients received the maximum dose before being converted to insulin. The majority of those who achieved glycemic control required low glyburide doses (2.5–5 mg/day). This finding may be a result of severity of disease and inadequate dosing or a maximum response effect for glyburide occurring at a relative low dose. Interestingly, 8 of 12 women who converted to insulin were not in adequate glycemic control by the time of delivery. This study demonstrated that not all patients achieve glycemic control with a single medication, even with insulin. The majority of clinical studies have reported that glyburide is similar to insulin in efficacy and safety when used for the treatment of GDM.[3,4,11,15,16] Such findings along with lower cost and ease of administration have led to the increased utilization of glyburide during pregnancy.

The FDA-approved dosage for glyburide in the treatment of non-pregnant patients with type 2 diabetes mellitus is 1.25–20 mg/day (in divided doses).[7] Optimizing timing of administration of glyburide in pregnancy might allow for lower dosages to be used, thereby minimizing risks to the fetus while at the same time maintaining efficacy. Glyburide peak concentrations usually occur 2–3 h following dosing in pregnant women.[17] Due to induction of metabolism, peak glyburide concentrations are much lower in pregnant women compared to non-pregnant women. Without changing dosage, one way to attempt optimization of glyburide efficacy would be to optimize timing of administration through achieving a simultaneous peak in glyburide concentration with postprandial peak glucose concentration. Oral glyburide administered approximately 1 h prior to a meal will maximize the effect of glyburide on the pancreas at the time it is most needed.[18]

Another approach to optimizing glyburide efficacy is to consider alternate glyburide dosage strategies. In previously published, randomized, gestational diabetes studies, glyburide dosage has ranged from 1.25 to 20 mg/day,[3,4] which is the same range used in the non-pregnant population. However, this dosage range has not been optimized for pregnant women.[17] Glyburide is metabolized by cytochrome P450 (CYP) enzymes (CYP2C9, CYP3A, and CYP2C19) in the liver and the intestines that are known to have altered activity during pregnancy. In our study,[17] evaluating the pharmacokinetics of glyburide in women with GDM, pregnant women had much lower concentrations than in non-pregnant control subjects given the same dose. In order to achieve similar concentrations to those seen in the non-pregnant population, pregnant women would need to take more than twice the dose. Given these results, it is possible that pregnant patients with inadequate glucose control may benefit from higher and more frequent dosing of glyburide. Nevertheless, it is important to be mindful that the safety of doses exceeding 20 mg/day in pregnancy has not been evaluated.

Our understanding of glyburide transfer to the fetus has been evolving. *In vivo* studies in pregnant rats have reported high maternal-to-fetal transfer of glyburide, resulting in