

The Role of Oral Agents in the Treatment of Gestational Diabetes

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Treatment of gestational diabetes is associated with improved maternal and neonatal outcomes. Besides diet and insulin, oral agents are often considered as options for therapy.

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that is first identified during pregnancy.¹ It complicates up to 7% of pregnancies in the United States.² GDM is diagnosed when 2 or more values meet or exceed recommended thresholds on a 100-g, 3-hour or a 75-g, 2-hour oral glucose tolerance test.

GDM is associated with multiple short- and long-term complications affecting the mother and her offspring (Table).³ Maternal hyperglycemia below the levels diagnostic of diabetes is associated with an increased risk for large-for-gestational-age (LGA) birth, primary cesarean delivery, neonatal hypoglycemia, preterm delivery, neonatal intensive care unit (NICU) admission, hyperbilirubinemia, preeclampsia, and shoulder dystocia or birth injury.⁴

The benefits of treating GDM with diet and insulin, if necessary, are well established based on 2 randomized trials that demonstrated improved maternal and neonatal outcomes. Crowther et al showed that treatment of GDM with diet and insulin as needed reduced the rate of serious perinatal

outcomes (1 or more of the following: death, shoulder dystocia, bone fracture, nerve palsy) compared to routine care (1% vs 4%) (relative risk [RR], 0.33; 95% CI, 0.14-0.75).⁵ Treatment was also associated with less gestational weight gain and lower rates of LGA birth, macrosomia, preeclampsia, and postpartum depression.

In a 2009 trial by Landon et al, patients assigned to the treatment group (nutritional counseling, diet therapy, and insulin as needed) had significant reductions in mean birth weight, LGA birth, birth weight above 4,000 g, neonatal fat mass, cesarean delivery, shoulder dystocia, preeclampsia, gestational hypertension, and gestational weight gain.⁶

The use of oral hypoglycemic agents in the treatment of GDM remains controversial. The American Diabetes Association (ADA) and the American College of Obstetricians and Gynecologists (ACOG) recommend insulin as the first-line agent for patients who fail medical nutrition therapy, and each group calls for further study to establish the safety of oral hypoglycemic agents.^{1,2} Furthermore, no oral agent is FDA-approved for the treatment of diabetes in pregnancy. Despite these concerns, a survey of nearly 1,400 ACOG members in 2004 showed that 13% used glyburide initially when medical nutrition therapy failed.⁷

GLYBURIDE

Glyburide, a category C sulfonylurea, increases insulin secretion, resulting in decreased hepatic glucose production and increased insulin sensitivity.⁸ Several randomized trials have compared glyburide to insulin for the treatment of GDM.

The largest study randomized 201 women to glyburide and 203 women to insulin.⁸

FOCUSPOINT

Although the use of oral antidiabetic agents has increased, none of the oral agents are FDA approved for use in pregnancy.

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TABLE. Health Risks of Gestational Diabetes³

MOTHER	FETUS	NEWBORN	CHILD/ADULT
Birth trauma	Hyperinsulinemia	Respiratory distress syndrome	Obesity
Increased cesarean delivery	Cardiomyopathy	Hypoglycemia	Type 2 diabetes
Preeclampsia/ Gestational hypertension	Stillbirth	Hypocalcemia	Metabolic syndrome
Type 2 diabetes	Large for gestational age/ macrosomia	Hypomagnesemia	
Metabolic syndrome	Birth trauma	Hyperviscosity	
		Polycythemia	
		Hyperbilirubinemia	
		Cardiomyopathy	

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Women in the insulin group received 0.7 units/kg 3 times daily, with weekly adjustments as needed. The starting dose of glyburide was 2.5 mg orally in the morning, increased weekly as needed to a maximum dose of 10 mg twice daily.

Daily blood glucose control was similar between the 2 groups, though 18% of women on glyburide had glucose values above the desired range. Maternal hypoglycemia (blood glucose <40 mg/dL) occurred more commonly in the insulin group (20.2%) than the glyburide group (2%; $P = .03$), while preeclampsia and cesarean delivery occurred with equal frequency. The rate of adverse neonatal events was similar between the 2 groups, including LGA birth, macrosomia, hypoglycemia, NICU admission, and perinatal mortality.

A Brazilian study from 2005 randomized 70 women with GDM to therapy with insulin ($n = 27$), glyburide ($n = 24$), and acarbose ($n = 19$).⁹ Insulin (0.7-0.9 units/kg/day) was provided 4 times daily, and glyburide was administered up to 20 mg daily. Similar glycemic control, average newborn weight, and rate of maternal hypoglycemia requiring admission were noted between the insulin and glyburide groups. Compared to the insulin group, the glyburide group experienced a significantly higher rate of neonatal glucose levels lower than 40 mg/dL (3.7% vs

33.3%; $P = .006$) and a nonsignificant increased rate of LGA birth (3.7% vs 25%; $P = .07$). Approximately 20% of patients on glyburide did not achieve adequate glucose control and were switched to insulin.

Similar maternal glycemic control, rate of maternal hypoglycemia, neonatal birth weight, and neonatal glucose levels were noted in a small randomized Indian study comparing glyburide ($n = 10$) to insulin ($n = 13$).¹⁰ Ogunyemi et al reported significantly higher clinic 2-hour postprandial glucose levels in the 48 patients randomized to glyburide compared to 49 patients receiving insulin; however, maternal hypoglycemia, cesarean delivery rate, and birth weight were similar.¹¹ Neonatal hypoglycemia occurred in 28% of the glyburide group versus 13% from the insulin group, but this finding was not significant. The cost of glyburide was about one-third the cost of insulin. Approximately 6% of patients failed glyburide therapy.

In a randomized trial comparing insulin to glyburide ($N = 82$), Lain and coworkers noted similar glycemic control, except for higher postdinner blood sugars in the glyburide group.¹² Nearly 7% of patients failed glyburide therapy. Multiple measures of neonatal adiposity were similar between the 2 groups, though the percentage of macrosomic neonates (>4 kg) was significantly

higher in the glyburide group (22% vs 2.4%; $P = .01$).

Glyburide fails to achieve adequate glycemic control in 6% to 20% of patients, based on the studies above. Risk factors for glyburide failure include maternal age of 34 or older, diagnosis of GDM before 25 weeks, 1-hour 50-gm glucose screen of 200 mg/dL or above, and gestational weight gain of 12 kg or higher.¹³⁻¹⁵

Glyburide transfer across the placenta is disputed. Glyburide was absent from umbilical cord blood in one study, while a more recent study, using a different isolation technique, reported umbilical cord glyburide levels to be 70% of maternal levels.^{8,16} Despite concerns regarding transplacental transfer, a recent meta-analysis reported that glyburide was not associated with an increase in adverse neonatal outcome.¹⁷

METFORMIN

Metformin, a category B biguanide that crosses the placenta, stimulates hepatic and peripheral glucose uptake and suppresses hepatic glucose production.¹⁸ In a large randomized trial from Australia and New Zealand, 733 women who failed dietary therapy for GDM were randomized to metformin (maximum daily dose, 2,500 mg) or insulin.¹⁹ The primary outcome, a composite of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score lower than 7, or prematurity, occurred with similar frequency in the 2 groups (32% in each group). Severe neonatal hypoglycemia (<28.8 mg/dL) occurred less commonly in the metformin group (8.1% vs 3.3%) (RR, 0.41; 95% CI, 0.21-0.78), while preterm birth occurred more commonly in women exposed to metformin (12.1% vs 7.6%) (RR, 1.60; 95% CI, 1.02-2.52).

Secondary outcomes such as maternal glycemic control, maternal hypertensive complications, LGA birth, neonatal anthropometric measures and umbilical cord insulin levels were similar between the 2 groups. Supplemental insulin was added to the metformin group (46.3% of women) in order to obtain adequate glycemic control.

Women requiring supplemental insulin had a higher BMI and higher baseline glucose levels. No difference in primary outcome rates were noted between women

treated with metformin alone and those treated with supplemental insulin. Significantly more women would choose metformin (77%) than insulin (27%; $P < 0.001$) in a subsequent pregnancy.

A recent Finnish study randomized 50 women to insulin and 47 to metformin (maximum dose, 750 mg 3 times daily).²⁰ Patients on metformin had a higher cesarean delivery rate, but mean birth weight and the incidence of LGA birth and neonatal morbidity were similar between the 2 groups.

Supplemental insulin was required in 32% of those taking metformin. Women needing supplemental insulin had a higher BMI and higher fasting glucose levels, and they required therapy earlier in pregnancy than women who were normoglycemic on metformin. They also delivered neonates with a higher average birth weight and trended towards an increased rate of LGA birth.

An American randomized trial comparing metformin ($n = 75$; maximum daily dose, 2 gm in divided doses) to glyburide ($n = 74$; maximum daily dose, 10 mg twice daily) in women with GDM revealed treatment failure in 34.7% of the metformin group and 16.2% of the glyburide group (odds ratio, 2.1; 95% CI, 1.2-3.9).²¹ Similar glycemic control was noted among the patients who achieved euglycemia on either oral medication.

The secondary outcome rates (eg, birth weight >4 kg, NICU admission, neonatal hypoglycemia, maternal hypoglycemia, shoulder dystocia, and preeclampsia) were similar between the 2 groups, while the rate of cesarean delivery was significantly higher in the metformin group (14.7% vs 2.7%; $P = .02$).

A 2010 Brazilian trial randomized 72 women with GDM who failed dietary therapy to glyburide ($n = 40$; initial dose of 2.5 mg twice daily increased up to 20 mg daily) or metformin ($n = 32$; initial dose of 500 mg twice daily increased up to 2,500 mg daily).²² Treatment failure was noted in 10 (23.8%) of the glyburide group and 8 (25%) of the metformin group ($P = 1.0$). Fasting and postprandial glucose levels were similar between the 2 groups. No differences in birth weight or the rate of cesarean delivery, LGA birth, macrosomia (>4 kg), and neonatal hypoglycemia (<40 mg/dL) were noted between the 2 groups. *(continued on page 28)*

FOCUSPOINT
Of the oral agents, glyburide is most effective in controlling blood glucose levels but fails in up to 20% of patients.

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ACARBOSE

Acarbose is a category B α -glucosidase inhibitor that inhibits glucose absorption from the upper gastrointestinal tract despite minimal systemic absorption.¹⁸ In a randomized controlled trial comparing insulin, glyburide, and acarbose, Bertini et al reported a 42% failure rate with acarbose (50 mg before meals, increased to a maximum total dose of 300 mg).⁹ Similar rates of macrosomia and maternal and neonatal hypoglycemia were noted between acarbose and insulin.

SUMMARY

The treatment of GDM is associated with decreased rates of maternal and neonatal complications. Insulin remains the gold standard for GDM therapy and is supported by the ADA and ACOG. Interest in the use of oral antidiabetic agents has increased over the past decade because of convenience and potential cost savings, though none of the oral agents are FDA approved for use in pregnancy. Of the oral agents, glyburide is most effective in controlling blood glucose levels but still fails in up to 20% of patients. Consistent evidence supporting an increased rate of maternal or neonatal adverse outcome associated with the use of glyburide, metformin, and acarbose is lacking.

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For a patient handout on diabetes, go to page 55. Patient handouts can also be accessed online at www.femalepatient.com/patienthandouts.aspx