Is metformin more effective than glyburide for treating gestational diabetes?

NO This randomized comparison of the two agents found metformin 2.1 times more likely to fail than glyburide was (95% confidence interval, 1.2–3.9). Neither drug may be preferable to insulin, however.

Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2010;115(1):55-59.

EXPERT COMMENTARY
Donald R. Coustan, MD, Professor of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Division of Maternal-Fetal Medicine, Women & Infants Hospital of Rhode Island, Providence, RI.

FAST TRACK

Metformin was 2.1 times more likely than glyburide to fail to control the glucose level

Gestational diabetes is on the increase in the United States. That trend will likely continue if recent recommendations by an international task force are adopted.[1,2] Those recommendations include a switch to a 75-g, 2-hour oral glucose tolerance test that meets or exceeds any of these thresholds: **1)** fasting, 92 mg/dL, **2)** 1 hour, 180 mg/dL, **3)** 2 hours, 153 mg/dL. Use of these new thresholds will increase the rate of gestational diabetes to about 15% of the population.

Traditionally, insulin has been prescribed to treat gestational diabetes when medical nutrition therapy fails to achieve the desired level of glucose control, but insulin must be administered by injection and carries the inherent risk of hypoglycemia if caloric intake is not appropriately matched. The oral agent glyburide, a sulfonylurea, also carries a risk of hypoglycemia. Another oral drug, metformin, a biguanide, carries no risk of hypoglycemia. It would be highly desirable if oral antidiabetic agents could be used in pregnancy.

Randomized trials of glyburide and metformin have demonstrated efficacy similar to that of insulin, although some treated patients needed additional insulin when predetermined maximal doses did not control the glucose level.[3,4]

In this latest trial, the two oral agents produced similar glucose levels among gravidas in whom either drug was effective. However, the failure rate of metformin (35%) was significantly higher than that of glyburide (16%). In this study, the likelihood of failure was similar to that described in the MiG trial for metformin (46%) and in a large case series for glyburide (16%).[5]

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

The temptation is great to use an oral agent instead of insulin to manage gestational diabetes. I urge caution about this strategy, however, until more is known about the potential fetal effects of those oral agents.

Insulin does not cross the placenta to a significant extent, and its use in pregnancy has withstood the test of time. The high likelihood that supplemental insulin will be needed when metformin is used, and the concentration of metformin in the fetal compartment make it a somewhat less attractive treatment option. And the recent evidence of transplacental passage of glyburide is disappointing.

I no longer prescribe glyburide routinely to treat gestational diabetes. When using it does appear appropriate—such as in a patient who refuses insulin despite a high glucose level—I make certain to document that she has been counseled about the unknown potential long-term effects on offspring. I also explain that no harmful effects have yet been found.

›› DONALD R. COUSTAN, MD

Do oral agents cross the placenta?

An important consideration in regard to these oral agents is safety. Although an in vitro study of isolated perfused placental cotyledons showed little transplacental passage of glyburide,[6] and the original randomized trial of glyburide[3] found that the drug could not be identified in cord blood of exposed newborns, a recent publication from the National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Unit Network demonstrated that the average fetal glyburide level was 70% of the maternal level.[7] Metformin also crosses the placenta and is concentrated in the fetal compartment, with the fetal level approximately double that of the maternal circulation.[8]

In published reports to date, no significant increase in adverse outcomes has been reported with metformin or glyburide. A number of questions remain unanswered, however.

For example, the role of in utero programming on the development of problems such as insulin resistance syndrome in later life has drawn a great deal of attention. Just as exposure to hyperglycemia in utero has been shown to predispose to the development of glucose intolerance[9] in adulthood, might exposure to an insulin sensitizer such as metformin, or an insulin secretagogue such as glyburide, have long-lasting effects on offspring? Studies of animal models are needed, as well as long-term follow-up of exposed humans, to establish the safety of these agents in gestational diabetes.

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