



Are oral hypoglycemic agents equivalent to insulin in treating gestational diabetes?

NO—although the authors of a systematic review and meta-analysis conclude that they are. In fact, the preponderance of the evidence is that insulin remains the *only* first-line therapy for gestational diabetes mellitus (GDM).

Dhulkotia JS, Ola B, Fraser R, Farrell T. Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010;203(5):457.e1-9.

► EXPERT COMMENTARY

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category are unlikely to produce a coherent conclusion. In this meta-analysis, clinical heterogeneity likely exists because glyburide and metformin have entirely different modes of action.

When viewed in isolation, glyburide looks less promising

Let's consider the literature on glyburide and metformin separately. All three studies comparing glyburide and insulin demonstrated a higher incidence of neonatal hypoglycemia among women taking glyburide, with one of those studies demonstrating a statistically significant effect. In contrast, the single large randomized, controlled study comparing metformin and insulin showed a non-significant reduction in the rate of neonatal hypoglycemia for women taking metformin. The combined effect of the oral agents in the meta-analysis is a nonsignificant increase in neonatal hypoglycemia, but the odds ratio is 1.59, which certainly has some clinical meaning. A similar clinical heterogeneity of the effect on birth weight is seen when the different oral agents are compared with insulin.

Overall, data on glyburide are confusing. Most studies find glyburide and insulin to be essentially equivalent for glycemic control, but insulin leads to better outcomes (although this effect is not significant, probably owing to insufficient power).⁴ The bias among many researchers exploring the use of glyburide for GDM is obvious. One study observed that glyburide was associated with

Although some still believe that GDM is a diagnosis looking for a disease, we have excellent evidence that the treatment of even mild forms of insulin resistance leads to improved maternal and neonatal outcomes.^{1,2} (See, for example, the article on GDM by E. Albert Reece, MD, PhD, MBA, on page 36 of this issue.) Treatment typically involves dietary modification, exercise, and, if necessary, injectable insulin. The most recent ACOG Practice Bulletin on GDM recommends that further studies be conducted before widespread use of oral hypoglycemic agents is initiated.³

The meta-analysis by Dhulkotia and colleagues compares “any” oral hypoglycemic agent (glyburide or metformin) with insulin and concludes that there is no difference between the two types of treatment. However, this conclusion can't be drawn from the existing literature, and it is certainly nonsensical to conduct a meta-analysis in which both types of oral agents are combined. Studies that lump different medications with distinct mechanisms of action into the same

FAST TRACK

The goal of treatment of gestational diabetes is to quickly achieve a state of euglycemia to minimize the effects of hyperglycemia on the fetus. Only insulin achieves this goal.



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a greater likelihood of neonatal hypoglycemia and higher birth weight than insulin, but still concluded that glyburide is a reasonable first-line therapy for GDM.⁵

Data on metformin are more promising.⁶ In the large prospective trial of metformin, the great majority of outcomes were essentially the same for both metformin and insulin. However, two findings give pause:

- Approximately half the patients randomized to metformin eventually needed insulin to achieve adequate glucose control
- There was a higher incidence of preterm birth (<37 weeks) in the metformin arm. Although neonatal complications did not occur at a statistically higher rate in the metformin group, the risk of preterm birth should certainly be mentioned to the patient before she is started on the medication.

Ease of use shouldn't trump safety concerns

Over the past decade, it has become increasingly common for health-care providers to prescribe an oral agent instead of insulin for glycemic control—even though insulin remains the standard of care. I note a prevailing perception that oral agents are easier to use than insulin, thereby improving compliance. Oral agents are easier to prescribe and do not require extensive teaching, which does save time, including nonreimbursable office time. As a result, it makes economic sense to prescribe a pill.

In my experience, however, most pregnant women are adherent with insulin therapy, and insulin injection can be reliably taught and appropriately performed regardless of the patient's socioeconomic status, education, or language. In terms of efficacy and safety, then, insulin remains our best option. ☹

References

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Given the limitations of the studies conducted so far, I believe that insulin should remain first-line therapy in the treatment of gestational diabetes. The goal of treatment is not to achieve good control *eventually*, as metformin does, but to *quickly* achieve a state of euglycemia to minimize the effects of hyperglycemia on the fetus.

Some subpopulations of women who have GDM may be adequately treated with metformin—but identifying them remains difficult. Until we can be certain of the benefit-risk profile of oral hypoglycemic agents in pregnancy, their use should be limited to clinical studies.

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Instant Poll



You are treating a woman who has gestational diabetes. Dietary modification and exercise are insufficient to bring her glucose under adequate control. In your practice, the next step is to:

- A) start insulin therapy
- B) start glyburide
- C) start metformin
- D) refer the patient to a provider who cares for high-risk patients

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