COMMENT ON NACHUM ET AL.

Glyburide Versus Metformin and Their Combination for the Treatment of Gestational Diabetes Mellitus: A Randomized Controlled Study. Diabetes Care 2017;40:332–337

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Given the increasing popularity of oral agents, we commend Nachum et al. (1) on their randomized controlled trial examining metformin or glyburide as a first-line agent to treat gestational diabetes mellitus (GDM) and adding or switching to the alternate agent for adverse events or failures. However, we question whether the study design and conclusions can be generalized to many GDM populations.

First, a GDM diagnosis was made at <24 weeks in 27 of 104 patients, suggesting impaired glucose tolerance predating the pregnancy in ~25%. An early GDM diagnosis increased the risk of failing glyburide by about eightfold in our series (2). A recent cohort also demonstrated that pregnancies with GDM diagnosed at 12–23 vs. ≥24 weeks were more likely to require insulin and neonatal intensive care admission (3). Were there differences in the efficacy of the two agents with GDM diagnosis at <24 weeks?

Another strong predictor of oral hypoglycemic failure is treatment of fasting hyperglycemia with glyburide (2). Glyburide is typically dosed preprandially ~30 min before meals because of its peak in 2–3 h. However, glyburide was also prescribed at 10 P.M. to treat fasting hyperglycemia. The authors do not specify the dosing protocol or number of glucose measurements available per patient weekly to determine efficacy, but dosing glyburide at bedtime increases the risk of nocturnal hypoglycemia when glyburide peaks. Given the unfavorable pharmacokinetics of glyburide to treat fasting hyperglycemia, we wonder how often hypoglycemia or failures occurred in those patients receiving glyburide for fasting hyperglycemia.

When glyburide was initiated first, 23% failed for efficacy and 11% for hypoglycemia; adding/substituting metformin resulted in an additional 50% achieving control. When metformin was initiated first, 28% failed and 2% had adverse gastrointestinal events, and adding/substituting glyburide resulted in 87% achieving control. The authors concluded that metformin might be a superior first-line agent. An alternative interpretation would be that metformin initially failed more often than glyburide and glyburide is more likely to be successful in achieving glycemic control (87%) when metformin fails. However, when glyburide fails, adding metformin will less often achieve control (50%).

The authors conclude that the combination reduced the need for insulin from 32% to 11% and that combination oral therapy demonstrates high efficacy. However, determining whether these drugs can be safely and efficaciously substituted for insulin would require the combination to be directly compared with insulin alone. Further, although both of these drugs cross the placenta, recent data suggest glyburide levels in newborns are usually very low (4) but metformin is concentrated in the fetal compartment. Although unanswerable by this article (1), using two drugs that cross the placenta in order to avoid insulin raises concerns about the potential long-term programming effects of fetal hyperinsulinemia (glyburide) and altered hepatic gluconeogenesis, insulin sensitivity, mitochondrial function, and cell cycle proliferation (metformin) (5). Although long-term risks are unstudied, it is unclear whether the short-term efficacies and adverse effects of glyburide/metformin individually or in combination would be different if limited to conventional use at >24 weeks and if glyburide were not dosed at bedtime to treat fasting hyperglycemia.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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