Glyburide: caution for efficacy and fetal programming effects

TO THE EDITORS: We read with interest the article of Lain et al., “Neonatal adiposity following maternal treatment of gestational diabetes with glyburide compared with insulin.” The authors concluded that glyburide and insulin are equally effective for treatment of gestational diabetes mellitus, with no difference in neonatal adiposity, suggesting that this adds “to the safety data for the use of glyburide during pregnancy.” However, an assessment of their results and an understanding of new data regarding glyburide and fetal programming suggest that these conclusions should be reassessed.

Consistent with the trend toward increased percent fat mass in the glyburide group, the infants in the glyburide group had borderline significant increased fat mass and fat-free mass, significantly increased birthweight (despite similar length and shoulder-elbow and hip-knee measurements). The chest and abdominal circumferences of the glyburide infants exhibited significant and near significant increases, respectively. Perhaps more importantly, the glyburide treatment was associated with a 4.9% \((P = .01)\) increase in the rates of intrauterine growth retardation (IUGR; less than the 10th percentile) and a 20% increase in the number of infants weighing more than 4000 g.

Clearly, these results do not suggest equivalency of glyburide and insulin. The authors acknowledged the study limitation of only 41 patients in each group, which resulted in a lack of sufficient power for many of the near significant differences in body composition.

In addition to the increased rates of macrosomic infants and the adipose measurements, there are new data to indicate that glyburide crosses the human placenta, resulting in fetal plasma concentrations approximating 70% that of maternal plasma levels. Because insulin is a potent fetal systemic and neurotrophic growth factor, glyburide-induced fetal insulin release may result in enhanced fetal growth, as well as potential unknown effects on fetal programming of offspring disease propensity. When coupled with the increased risk for IUGR and infants weighing more than 4000 g, the knowledge of transplacental glyburide transfer and the potential for long-term impact on fetal programming should raise caution before the rapid adoption of sulfonylurea use during pregnancy.

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REFERENCES


REPLY

We thank Drs Ross and Kjos for their interest in our study. We agree that data regarding placental transport of glyburide are important for safety and efficacy information regarding the use of glyburide during pregnancy.

Our study was an equivalency trial between glyburide and insulin, evaluating neonatal adiposity measured by total body electric conductance (TOBEC). We demonstrated no difference in the primary outcome: neonatal percent fat mass. TOBEC was utilized, because percent fat mass better identifies subtle differences in body composition compared with birthweight or birthweight percentiles. In our study, there was a difference in the distribution of percentile by weight (<10%, for appropriate for gestational age, and >90%; \(P = .01\)) and macrosomia \((P = .01)\), but these measures are less precise measures of adiposity. Percentiles are flawed, because they are population and time specific and do not describe growth rate or growth potential. Furthermore, not all neonates at the extremes of size are pathologically small or large.

In addition, any individual skinfold or circumference measure is limited compared with composite measures such as skinfold sum or arm fat area. Finally, fat mass and fat-free mass are correlated with birthweight and will increase with overall increasing weight. Importantly, however, the percent fat mass of each neonate, our primary outcome, was not different between groups. Individual and composite measures were in-