births each year, this might prevent 10,000 brachial plexus injuries annually. This seems like a worthwhile endeavor to work on at the hospital level in terms of quality improvement. In fact, what if having providers participate in shoulder dystocia became a process measure for quality improvement? This seems like a potentially worthwhile metric, if feasible, that would augment the ability to improve outcomes for women and babies.—ABC)

Metformin Use in Pregnancy: Promises and Uncertainties

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ABSTRACT

Metformin has been prescribed in pregnancy for more than 40 years, but it is since its increased use in polycystic ovarian syndrome treatment that exposure of the fetus to metformin in early pregnancy and its safety for both mother and child have been investigated more robustly. This review discusses the history, key trials, and controversies associated with metformin use in pregnancy. Metformin appears to be safe for use in early pregnancy, and findings do not suggest an increase in congenital malformations or miscarriages associated with its use. Short-term outcomes comparing metformin to insulin for treating gestational diabetes from trial and meta-analysis findings support its use, but there are fewer long-term and safety outcome data in this setting. In addition, there is not enough evidence to recommend its use as an additional agent for managing diabetes mellitus type 2 in pregnancy.

Reassuringly, in follow-up of offspring, children exposed to metformin in utero have not shown to have any difference in total fat mass, body fat percentage, and in blood pressure or any significant differences in motor, social, and linguistic development. These studies are, however, limited in terms of size and length, and hence, there are lingering concerns about potential long-term effects of metformin exposure in utero as the drug readily crosses the placenta. Studies suggest that metformin use may not affect early human embryos, but it may indirectly affect fetal development through altered nutrient delivery or placental growth. Metformin use in pregnancy internationally has shown to have increased in recent times, but it appears quite varied between countries. There is a need for further data and clear evidence on the long-term effects of metformin use and further research in the management of medical conditions in pregnancy.

EDITORIAL COMMENT

(Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy. Whereas in a normal-weight, white cohort, the risk of GDM is perhaps 3% to 4% or less, in overweight or obese women (which now comprise >60% of pregnant women) and in women who are Hispanic, Asian or Pacific Islander, or Native American, the risk of GDM is higher, and in some of these populations, rates can be greater than 15% (Paediatr Perinatal Epidemiol 2015;29:436–443). Gestational diabetes mellitus is associated with numerous pregnancy complications including preeclampsia, preterm birth, stillbirth, cesarean delivery, fetal macrosomia, birth injury, neonatal hypoglycemia, childhood obesity in the offspring, and other short- and long-term complications (BMC Pregnancy Childbirth 2016;16:231; Diabetes Care 2016;39:75–81). Many of these complications appear to be associated with hyperglycemia, so tight control of maternal plasma glucose is the primary approach to management during pregnancy. The first-line approach is usually a strict carbohydrate-controlled diet and exercise. The exercise does not have to be aerobic, necessarily, as even frequent walking throughout the day can be beneficial (Appl Physiol Nutr Metab 2008;33:511–517).
If such lifestyle modifications fail to control maternal glucose values, medical therapy is indicated. For decades, injectable insulin has been the primary approach. Unfortunately, injectable insulin can be challenging to use. It must be stored, drawn up in a syringe, and injected, and patients are often nervous about its use. Thus, there have been attempts to identify an oral agent that will produce similar outcomes. The first medication that was widely adopted was glyburide. This widespread adoption came after the *New England Journal of Medicine* published a randomized trial that, although it demonstrated no statistical difference in the outcomes, was underpowered to do so (*N Engl J Med* 2000;343:1134–1138). A number of other trials have been conducted, some of them with worse outcomes in the offspring delivered to women randomized to glyburide. Finally, in 2015, a meta-analysis demonstrated that a number of outcomes are worse in women randomized to glyburide, and a number of national organizations are discouraging the use of glyburide for first-line treatment of GDM because of these findings (*BMJ* 2015;350:h102). Specifically, the American College of Obstetricians and Gynecologists did so in a recent practice bulletin (*Obstet Gynecol* 2017;130:e17–e37).

However, metformin has also undergone study, and in a 2008 adequately powered randomized trial, there were no differences in outcomes between pregnancies treated with metformin versus insulin (*N Engl J Med* 2008;358:2003–2015). However, at that time, perhaps because glyburide was being used widely at that point, most practices did not adopt metformin. The other concerns with metformin are (1) it freely crosses the placenta, and the research regarding its impact on the developing human fetus is not extensive, and (2) there have been findings of an increased risk of preterm birth in women assigned to metformin in clinical trials. In addition, in the 2008 study, more than half of the women randomized to metformin ended up on insulin. There have not been as many trials of metformin as glyburide versus insulin, but the 2015 *BMJ* meta-analysis did identify several, and from that study, there were no significant differences in the short-term outcomes between insulin and metformin.

The current review abstracted above from *Diabetologia* reviews the data regarding metformin use in pregnancy. As described above, in the setting of GDM, when compared with insulin, there were no statistically significant differences in clinical outcomes usually related to GDM between the 2 drugs. In addition, there have been no statistical differences in medium-range metabolic or neurodevelopmental outcomes in the offspring, which is encouraging. However, the authors do call for continued study and particularly to examine long-term outcomes in the offspring. Further, in addition to its use in GDM, metformin may have benefits for women with diabetes mellitus type 2, but there are limited data. Recently, a study demonstrated that metformin in obese women reduced the risk of preeclampsia from 11% to 3% (*N Engl J Med* 2016;374:434–443).

Thus, we have a good potential candidate for an oral agent to treat GDM in metformin. In our practice, we have introduced its use, particularly in women who appear to have a milder form of A2GDM with the thought that the failure rate will be lower. Because of the odd finding of an elevated risk of preterm birth, we do counsel about that risk. But, it is unfortunate that there are not several large trials of this medication with long-term follow-up planned. Pregnant women and their neonates deserve the same attention and consideration by drug companies as other patients. Unfortunately, the concern of impacting the fetus leads companies to be quite skittish, and it is commonly not until a drug is off of patent that there is enough experience for its use in pregnant women, thus no strong incentive for a particular drug company to study it. Thus, it falls to the obstetric research community. One hopes that one of the large research consortiums will take on this research question to provide better information for the many women affected by GDM.—ABC