EDITORIAL (SEE ROWAN ET AL., P. 2279)

Metformin Therapy During Pregnancy

Good for the goose and good for the gosling too?

Type 2 diabetes and gestational diabetes mellitus (GDM) are closely related disorders characterized by increased insulin resistance. Metformin, a biguanide compound, exerts its clinical effect by both reducing hepatic glucose output and by increasing insulin sensitivity. This results in a decreased glucose level without an associated high risk of either hypoglycemia or weight gain. These characteristics have established metformin as an ideal first-line treatment for people with type 2 diabetes and, hypothetically, a particularly attractive drug for use in pregnancy. However, metformin is known to cross the placenta (1,2), and its use in pregnancy has been limited by concerns regarding potential adverse effects on both the mother and the fetus.

Historically, some of the earliest reports of the use of metformin during pregnancy have come from South Africa, where it has been used since the late 1970s for women with both type 2 diabetes and GDM (3–6). While perinatal mortality for these women was still higher than that seen in the general obstetric population, it was nonetheless lower than in women who had gone untreated and similar to those who were changed to insulin. No "headline" adverse events or side effects were reported.

Confidence regarding the use of metformin in pregnancy has been reinforced by the results of several observational studies and randomized trials over the past decade. Two meta-analyses of observational studies—one of women using metformin and/or sulphonylureas and one of women using metformin alone during the first trimester—did not show an increase in congenital malformations or neonatal deaths (7,8). While increased perinatal mortality and pre-eclampsia was noted in one study of 50 women with type 2 diabetes using metformin, these results may have been confounded by other factors including the fact that women taking metformin were more obese than those taking insulin (9). In another cohort of women with type 2 diabetes, maternal/fetal outcomes were as good in women using metformin as those on insulin alone, even though women in the metformin group were at higher risk of poor outcomes (10). In a more recent analysis of 379 women with type 2 diabetes using oral hypoglycemic agents between 1991–2000, again in South Africa, increased perinatal mortality was associated with the use of sulphonylureas or sulphonylureas plus metformin, but not with metformin alone (11).

A higher level of evidence has come from randomized clinical trials using metformin in the treatment of women with GDM. In the Metformin in Gestational Diabetes (MiG) trial, the largest study so far reported of metformin use in women with GDM, 751 women were randomized to receive either metformin or insulin (12). There was no significant difference in the composite fetal outcome between the two groups although preterm birth was found to be increased in the metformin group. Women in the metformin group had less weight gain compared with women in the insulin group. The results provide further evidence regarding the safety of metformin in pregnancy. A comparable, but much smaller, randomized trial of 63 patients found similar results (13).

Considerable research has been done on the use of metformin in women with polycystic ovary syndrome (PCOS) around the time of conception and during pregnancy, yielding useful data regarding the safety of this drug. A number of these studies have evaluated metformin for use in ovulation induction and infertility in this population (14,15). Similar to the studies in women with type 2 diabetes, the use of metformin early in pregnancy in women with PCOS has not indicated harm and has suggested potential benefit. While the metformin-induced reduction in insulin resistance in women with PCOS should in theory also lower the risk of developing GDM, the limited results so far have been conflicting (16,17).

Randomized trials are underway looking at metformin's possible benefit in obese women and women with type 2 diabetes during pregnancy. The Metformin in Obese Nondiabetic Pregnant Women (MOP) trial is a multicentered, randomized trial of 2,178 obese pregnant women randomized to receive either metformin or placebo with a primary outcome of birth weight centile (ClinicalTrials.gov). This study will examine whether metformin should play a role in obese nondiabetic women during pregnancy. The Metformin in Women with Type 2 diabetes in Pregnancy (MiTy) trial is currently randomizing 500 women with type 2 diabetes in pregnancy to receive metformin or placebo in addition to their usual regimen of insulin (ClinicalTrials.gov). The primary outcome is a composite fetal outcome. This study will clarify whether adding metformin to insulin in women with type 2 diabetes will be beneficial to the mothers and infants.

There is increasing evidence that infants exposed to diabetes in utero have an increased incidence of childhood obesity and diabetes (18,19). Infants of women with diabetes who were born large for gestational age have been found to have increased insulin resistance when compared with infants born of appropriate size for gestational age (20). Such insulin resistance may lead to or be the result of epigenetic changes in utero and set the infant up for long-term alterations in fetal fat distribution and metabolic changes.

It is possible that infants of diabetic mothers exposed to metformin in utero may experience a reduction in insulin resistance. This may in turn have beneficial effects on adipose tissue distribution and the inflammation associated with insulin resistance. Preliminary data on this question is contained in the article by Rowan et al. (21) in this issue of *Diabetes Care*. In this first follow-up of the MiG study, infants of women with GDM who had been randomized to receive either metformin or insulin during pregnancy have been examined at 2 years of age. Evaluation of these infants offers a unique opportunity to examine the effects of metformin free of the bias of observational studies of nonrandomized cohorts. Rowan et al. found that the offspring exposed to metformin in utero had increased subscapular and biceps skinfolds when compared with the unexposed infants, while total body fat was similar. They hypothesized that this represents a possible benefit as this may signal a healthier fat distribution. Longer term studies will examine the question of

"whether children exposed to metformin will develop less visceral fat and be more insulin sensitive" (21).

Scientists have postulated that the major determinant of body fat distribution is insulin resistance (22). Normally, fat is deposited in subcutaneous adipose stores. It is hypothesized that as fat stores increase, so does insulin resistance, limiting further deposition in the subcutaneous stores. This leads to increased uptake of triglycerides into visceral stores and other ectopic sites such as hepatic sites and others. If in fact the increase in subcutaneous fat indicates less visceral and ectopic fat in these infants (not yet demonstrated), this may signal reduced insulin resistance and long-term benefit from in utero metformin exposure. We must be mindful that the earliest effects of diabetes in pregnancy on childhood obesity often do not become manifest until after 6–9 years of age (18,23). Hence, longer follow-up studies will be required to determine the impact of in utero metformin exposure on the development of obesity and the metabolic syndrome in offspring.

Clinical experience and the evidence published thus far support the safety and efficacy of metformin use in pregnancy with respect to the immediate pregnancy outcomes. However, does the use of metformin in pregnancy ultimately have a beneficial, neutral, or deleterious effect on the offspring? While the results of Rowan et al. (21) on this issue are both encouraging and reassuring, and the possibility of benefit in children and adolescents with in utero exposure to metformin is intriguing, the long-term impact—positive or negative—of metformin use is still largely an unknown quantity. This work is the first of several necessary steps toward answering this important question.

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