Metformin for Gestational Diabetes Mellitus: Progeny, Perspective, and a Personalized Approach

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Given the rapidly growing population of women diagnosed with gestational diabetes mellitus (GDM), approximating 1 in 7 pregnancies globally (1), in conjunction with the rising cost of insulins and lack of affordability (2), the popularity of using an oral agent such as metformin is expanding enormously. In fact, a number of organizations have supported its use as an alternative to insulin (3–6). However, recent long-term studies on offspring have provided conflicting results, with two of three studies recently published on the 4- to 9-year-old children of mothers with GDM or polycystic ovarian syndrome (PCOS) suggesting some long-term metabolic programming effects on the offspring (7–9). This has given some clinical investigators and organizations (10,11) pause in embracing metformin as equivalent to insulin (12–17).

In the short term, there is an abundance of evidence that metformin has a safe track record and may have some benefits compared with insulin or glyburide when used for the treatment of GDM (18). Metformin is not teratogenic, with reassuring data for use in the first trimester (19–21), and in several meta-analyses, women with GDM randomized to metformin (often used with insulin) had less gestational weight gain, less gestational hypertension, and fewer infants who were large-for-gestational age (LGA) or with macrosomia (birth weight >4,000 g), and their infants had less neonatal hypoglycemia, than those randomized to insulin or glibenclamide (glyburide) therapy (22–24). However, metformin has a high failure rate, and 46% of women randomized to metformin needed to add insulin in the Metformin in Gestational Diabetes (MiG) randomized controlled trial (RCT) (25). In comparison, in a large multisite RCT in which insulin was compared with glyburide for GDM, the failure rate of glyburide was 18% (26). Important in interpreting RCT data is that glyburide was often not dosed according to its pharmacokinetic properties given the insulin peak from glyburide does not occur until 3–4 h after dosing, similar to regular insulin (13,27). Dosing glyburide at the same time of a meal or at bedtime to treat fasting hyperglycemia instead of 30 min to 1 h before meals may cause maternal hypoglycemia 3–4 h later, poor 1-h postprandial control, or nocturnal hypoglycemia and an inability to titrate up the dose (28). However, this may not be the only cause of more neonatal hypoglycemia compared with insulin. In an RCT of glyburide versus insulin, blood sugars were better in the glyburide group in spite of titration inflexibility (after taking out those who switched to insulin), but there was still increased neonatal hypoglycemia compared with insulin. Glyburide also crosses the placenta, although less so than metformin, and it is possible that if fetal concentrations are sufficient, glyburide could directly stimulate the fetal β-cells and cause fetal hyperinsulinemia (13,26). The pharmacokinetics of both metformin and glyburide during pregnancy may also influence results. In most trials, the usual dose of metformin was ~1 g b.i.d. and that of glyburide was ~5 mg b.i.d., and the concentrations of metformin and glyburide in pregnant women are ~80% and ~50%, respectively, of those in nonpregnant women due to increased clearance (28,29).

Two recent Cochrane meta-analyses concluded that the evidence comparing insulin with either metformin or glyburide was low-to-moderate quality and that there were no clear benefits for one agent above the other. Pregnancy outcomes and failures among agents are likely influenced by physician or maternal preference, availability, severity of GDM, and dosing practices (30,31). Unlike insulin, metformin does not reduce maternal triglycerides, an increasingly recognized substrate for fetal fat accretion (32) that was related to fetal growth in the MiG trial

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(33), and it should not be used if the fetus is at risk for an ischemic environment including placental insufficiency, hypertension, preeclampsia, or growth restriction (12,13,15,16). Interestingly, some data suggest that metformin may, in part, prevent the development of preeclampsia potentially by improving angiogenesis (34,35). Currently, metformin is being studied in two RCTs—Metformin in Women With Type 2 Diabetes in Pregnancy (MiTy) and Medical Optimization of Management of Type 2 Diabetes Complicating Pregnancy (MOMPOD)—for use in women with type 2 diabetes to determine if the addition of metformin to insulin in this population can reduce adverse neonatal outcomes as well as lower maternal insulin doses and maternal weight gain (36,37). Five RCTs using metformin in women with obesity alone or PCOS demonstrated a modestly lower gestational weight gain, but metformin was unsuccessful in preventing GDM, LGA, preterm birth, cesarean delivery, or hypertensive disorders (38–43).

With respect to long-term outcomes in offspring exposed to metformin, there are limited data to date. The largest RCT to date is the MiG trial, which randomized 750 women with GDM to receive either metformin or insulin during pregnancy (25). They subsequently reported on 2-year and 7- to 9-year offspring outcomes (7). At 2 years of age, the 318 offspring in the MiG trial (42% of the total cohort) demonstrated evidence of higher subcutaneous fat, but there was no difference in total fat mass in a subset (44). No measure of visceral fat was given (45) and no differences were found in neurodevelopmental outcomes. At 7–9 years of age, 208, or 28% of the original cohort, were assessed. Overall, there were no differences in the total cohort; however, when the results were reported according to the Adelaide (Australia) or Auckland (New Zealand) center at which they were randomized (7), differences emerged. The metformin-exposed offspring from Adelaide demonstrated a higher rate of LGA compared with those exposed to insulin alone (20.7% vs. 5.9%), and their mothers had higher fasting glucose levels during pregnancy, suggesting poorer glycemic control in utero. However, at 7 years, the Adelaide subgroup (n = 109) showed no differences in offspring weight or body composition. In contrast, the Auckland subgroup (n = 99) showed no differences in LGA rates for metformin compared with insulin at birth, but at 9 years the metformin-exposed group was heavier, had higher arm and waist circumferences, and higher waist:height ratios ($P < 0.05$), and they trended toward a higher BMI, triceps skinfold thickness, and abdominal fat volume by MRI (all P = 0.05). There were no differences in glucose, lipids, insulin resistance, or liver function test measures in either group. Interpretation is difficult given the limitations in follow-up, potential differences in glycemic control, use of insulin in 46% of the total cohort, and unknown postnatal effects that can markedly influence obesity risk in children. However, as in the animal literature, this highlights that there are conflicting reports on the offspring benefits and risks of using metformin in pregnancy.

In RCT studies examining offspring of women with PCOS treated with metformin versus placebo, the offspring of mothers treated with metformin weighed more at 1 year of age (46), and in a small, very limited study of 25 offspring followed at 8 years of age, higher fasting glucoses and a trend to higher systolic blood pressures were seen in the metformin-exposed group (47). In a recent publication, investigators analyzed 182 offspring at 4 years of age (55% of the total cohort) from two RCTs of women with PCOS (8). Children exposed to 1,700–2,000 g of metformin while in utero had higher weight and BMI z scores and twice the risk of overweight and obesity compared with those exposed to placebo. This was also an RCT, but there was no adjustment for potential confounders such as baseline socioeconomic status, ethnicity, or GDM in their model, although according to investigators, adding maternal BMI did not change the outcome. A systematic review and meta-analysis of 10 RCTs of 778 children of mothers with GDM or PCOS randomized to metformin versus insulin or placebo, which included the above trials, concluded that prenatal metformin was associated with increased offspring weight but not height or BMI (17).

On the other hand, a recently published large, population-based cohort study from New Zealand of 3,928 pregnancies in women with GDM, including 1,996 GDM women treated with metformin and 1,932 treated with insulin, identified by pharmaceutical claims data, showed no difference in weight-for-height z scores or risk of overweight (>85th percentile for weight for height). Further, there were no differences in behavioral assessments in offspring at 4 years of age after adjustment for maternal age, race/ethnicity, socioeconomic status, BMI, smoking, history of GDM, and timing of GDM diagnosis and treatment (9). The main limitations were that this information was not based on RCTs; 20% of the mothers who received metformin were also given insulin; there was missing growth data for 20% and professionally administered neurodevelopment questionnaires for 50%; no information was given on glycemic control, dosing, or the decision to prescribe metformin versus insulin; and 30–40% of the children at 4 years old were >85th percentile for weight. However, there were no differences between missing data in the metformin and insulin groups and outcomes were available for a very large sample of >3,000 children.

What might be the mechanisms by which metformin could result in a programming effect that later increases the risk for higher offspring weight? Outside of pregnancy, metformin has been shown to have anticancer effects, growth inhibitory properties, and β-cell and gluconeogenic effects and also to suppress mitochondrial respiration (12,13,15–17). Metformin is transported by organic cation transporters into mitochondrial membranes, present abundantly in both the fetus and placenta, and fetal metformin levels are similar to maternal levels. During early gestation, the embryo has few and relatively immature mitochondria and expresses very low levels of organic cation transporters, making metformin likely safe in the first trimester. In contrast, the placenta and fetus express metformin transporters, exhibit high rates of aerobic metabolism, and are dependent on mature mitochondrial activity in the second and third trimesters critical for fetal growth and nutrient transport (12,15,16). Metformin inhibits mitochondrial respiratory complex I of the electron transport chain, leading to decreased ATP production and increased AMP:ATP ratios. Metformin activates AMPK and inhibits the mechanistic target of rapamycin (mTOR) pathway, resulting in a decrease in proliferation, suppression of protein synthesis, and increases in apoptosis and

cell-cycle arrest. mTOR is a primary nutrient sensor in the placenta and its inhibition could attenuate nutrient flux and fetal growth (48). Metformin may also theoretically have antigrowth effects on pancreatic β-cell mass, impair glycolysis and the tricarboxylic acid cycle, inhibit thiamine uptake, and alter histone acetylation resulting in epigenetic modifications. These effects could have consequences for fetal growth, differentiation, and, potentially, childhood development, especially if relative nutrient restriction in utero is followed by the offspring later being exposed to an obesogenic environment. Metformin has been shown to modify the microbiome, which could alter gut serotonin levels, increase lactate delivery to the liver, and increase glucagon-like peptide 1. Interestingly, metformin increases gut glucose utilization and decreases serum glucose levels even when not absorbed (12,13,15,16), supporting the further testing of poorly absorbed preparations to reduce glucose while minimizing fetal exposure (49).

What can we conclude from the new follow-up offspring information from the above trials, and how should it affect our management in the face of limited resources, rising costs of insulin, and challenges in safely prescribing insulin in an ever-growing population of GDM mothers? Metformin has the potential to inhibit mitochondrial activity and result in relative nutrient restriction that could adversely affect function, growth, or differentiation of fetal or placental tissues, possibly increasing obesity risk later when the offspring is postnatally exposed to an obesogenic environment. However, there is no evidence that metformin causes small-for-gestational-age infants, and it is unknown if metformin causes these fetal effects in humans. Furthermore, interpretation of follow-up studies is complicated given limited offspring follow-up and negligible data on other postnatal influences that promote childhood obesity. GDM, like type 2 diabetes, is a heterogeneous disorder with variability in hepatic, adipose tissue, and skeletal muscle insulin resistance as well as β-cell dysfunction, resulting in a wide distribution of glycemic patterns that are not all effectively targeted by the same agent (50). Importantly, failure rates of metformin and glyburide are highest with a diagnosis of GDM earlier in gestation (<25 weeks), higher fasting glucose (>110 mg/dL [6.1 mmol/L]), higher A1C (>5.7%), higher maternal BMI, older age (>30 years), and a previous history of GDM (51,52). Metformin may be particularly useful in women at high risk for hypoglycemia, women who want to limit maternal weight gain, or those with an inability to afford or use insulin safely, especially in those with mild hyperglycemia. A less costly approach to treat more severe fasting hyperglycemia is to use NPH insulin immediately before bedtime, as it typically peaks 7–8 h later and is substantially less costly than newer basal insulins. Combining metformin and glyburide has been reported, but use of two agents that cross the placenta and may have programming effects of unknown long-term consequence (53) should be limited to circumstances when insulin is not a viable option.

Carefully controlled studies that appropriately target the use of oral agents according to individual patterns of hyperglycemia, optimize dosing according to their pharmacokinetic properties, and follow offspring long-term health outcomes are critical. In the meantime, a personalized approach to therapy to better meet the biological, psychosocial, and socioeconomic needs of individual patients is suggested, rather than unconditionally recommending one agent over the other in all patients. The current state of the science is reassuring in the use of metformin for mild GDM with respect to short-term pregnancy outcomes. However, patients should be counseled on the limited long-term safety data and conflicting data on adverse childhood metabolic effects. Fundamentally, inadequately controlled hyperglycemia, significant maternal hypoglycemia, and the inability to afford and safely use treatments pose even greater risks to both mother and baby.

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