A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes

Linda A. Barbour, MD; Christina Scifres, MD; Amy M. Valent, DO; Jacob E. Friedman, PhD; Thomas A. Buchanan, MD; Donald Coustan, MD; Kjersti Aagaard, MD, PhD; Kent L. Thornburg, PhD; Patrick M. Catalano, MD; Henry L. Galan, MD; William W. Hay Jr, MD; Antonio E. Frias, MD; Kartik Shankar, PhD; Rebecca A. Simmons, MD; Robert G. Moses, MD; David A. Sacks, MD; Mary R. Loeken, PhD

The Society for Maternal-Fetal Medicine (SMFM) recently endorsed metformin "as a reasonable and safe first-line pharmacologic alternative to insulin" for the treatment of gestational diabetes mellitus (GDM), and stated that "concerns have been raised for more frequent adverse neonatal outcomes with glyburide."[1] Although there is a large body of data supporting the short-term safety of using metformin, there are several points that deserve further consideration before endorsing metformin as a safe first-line alternative to insulin. First, unlike insulin, which in commonly used doses is not transported to the fetus,[2] metformin is transported across the placenta and achieves fetal concentrations equivalent to maternal. Hence, metformin has the potential to act on placental and fetal tissues.[3] Second, metformin has multiple effects, including suppression of mitochondrial respiration, growth inhibition, and effects on gluconeogenic responses that may impact both fetal and childhood development.[4,5] Of high clinical relevance, 2 long-term follow-up analyses from earlier randomized controlled trials (RCT), published after the SMFM statement, suggest that metformin-exposed offspring from mothers with polycystic ovary syndrome (PCOS) or GDM may weigh more, and manifest larger waist circumferences and higher fat mass at ages 4 years and 9 years.[6,7] Third, this recommendation implies that metformin is superior to other oral agents such as glyburide. However, common misuse of glyburide according to its pharmacokinetic properties deserves consideration, as does the paucity of data directly comparing oral agents. These are among the reasons that warrant reservation in using oral agents during critical periods of fetal development and challenge the stated superiority of metformin over glyburide.

Metformin has a multitude of intracellular effects and is currently the focus of much investigation in nonpregnant individuals due to its anticancer effects, growth inhibitory properties, and suppression of mitochondrial respiration.[5,8] During early gestation, the embryo has few, and relatively immature, mitochondria due to low rates of aerobic compared to anaerobic metabolism. Correspondingly, the embryo expresses very low levels of organic cation transporters, the transporters that transport metformin into cells and mitochondria.[9,10] Therefore, metformin is likely safe in the first trimester. In contrast, the placenta and fetus do express metformin transporters, exhibit high rates of aerobic

From the Divisions of Endocrinology and Maternal-Fetal Medicine, Departments of Medicine and Obstetrics and Gynecology, University of Colorado, Anschutz Medical Campus, Aurora, CO (Dr Barbour); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, OK (Dr Scifres); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology (Drs Valent and Frias), and Department of Medicine, Knight Cardiovascular Institute (Dr Thornburg), Oregon Health and Science University, Portland, OR; Divisions of Neonatology, Endocrinology, and Reproductive Sciences, Departments of Pediatrics, Medicine, Biochemistry, and Molecular Genetics, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO (Dr Friedman); Division of Endocrinology and Diabetes, Department of Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, CA (Dr Buchanan); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Alpert Medical School, Brown University, Providence, RI (Dr Coustan); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Baylor College of Medicine and Texas Children's Hospital, Houston, TX (Dr Aagaard); Department of Reproductive Biology, Center for Reproductive Health, Case Western Reserve University at MetroHealth Medical Center, Cleveland, OH (Dr Catalano); Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, CO (Dr Galan); Division of Neonatology, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO (Dr Hay); Arkansas Children's Nutrition Center, Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR (Dr Shankar); Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine Philadelphia, Philadelphia, PA (Dr Simmons); Illawarra Area Health Service, Wollongong Hospital, Wollongong, Australia (Dr Moses); Department of Research and Evaluation of Nutrition and Metabolism, Kaiser Permanente Southern California, Pasadena, CA (Dr Sacks); and Section on Islet Cell and Regenerative Biology, Joslin Diabetes Center, Department of Medicine, Harvard Medical School, Boston, MA (Dr Loeken).

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Corresponding author: Linda A. Barbour, MD. Lynn.Barbour@UCDenver.edu

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metabolism, and are dependent on mature mitochondrial activity in the second and third trimesters. A robust metabolic capacity of the placenta is critical for fetal growth and is necessary for nutrient and oxygen transport and pregnancy-sustaining steroid production.[11,12] Metformin inhibits mitochondrial respiratory complex I of the electron transport chain, leading to decreased ATP production and increased AMP:ATP ratios.[13] Although there is not current evidence of a detrimental effect, metformin has the potential to inhibit mitochondrial activity and may adversely affect function, growth, or differentiation of fetal or placental tissues into which metformin is transported.[14] Increased AMP:ATP ratios stimulate AMP-activated protein kinase (AMPK) activity. Among the effects of AMPK is to inhibit the mechanistic target of the rapamycin (mTOR) pathway, which reduces protein synthesis and cell proliferation and induces apoptosis and cell-cycle arrest.[13] The mTOR signaling pathway is a major nutrient-sensing mechanism in the placenta. Metformin's effect on mTOR could restrict nutrients, especially glucose and amino acids, to the fetus and placenta.[15,16] It has long been recognized that nutrient restriction during fetal development can program adult diseases such as type 2 diabetes, obesity, and cardiovascular disease.[17,18] Independent of AMPK activity, metformin inhibits production of tricarboxylic acid—derived metabolites needed for biosynthesis and growth and competitively inhibits thiamine transport, which is needed for mitochondrial activity.[9,19,20] What may be interpreted as a favorable growth effect attributed to improved maternal glycemic control could be, in part, due to growth inhibition by metformin in both the fetus and placenta. The long-term impact of such potential effects are unknown.

Metformin can compete for transport of the organic cation, choline, which can provide substrate for 1-carbon metabolism. It can inhibit both mitochondrial and cytosolic 1-carbon pathways, mimicking the "methyl folate trap" that can be caused by vitamin B_{12} deficiency.[21−23] Inhibition of 1-carbon metabolism can lead to decreased methionine, and S-adenosylmethionine that is needed for epigenetic modification of DNA and histones, resulting in decreased glutathione and increased homocysteine. These changes increase oxidative stress and decrease de novo synthesis of purines and pyrimidines.[21,22] Vitamin B_{12} deficiency during fetal development may result in insulin resistance and adiposity in children.[24] Of note, vitamin B_{12} deficiency is not uncommon in adults receiving metformin.[25] While these metformin effects may be beneficial for inhibiting cancer cell growth at concentrations that may be higher than plasma concentrations during treatment of GDM,[20] the potential for down-modulation of cell proliferation, inhibition of 1-carbon metabolism, suppression of mitochondrial-dependent biosynthesis, signaling that mimics nutrient and vitamin B_{12} deficiency, and effects on fetal gene expression may adversely affect fetal development and have long-term effects to program metabolic disease in the offspring.

Metformin has the potential to impair glucose-stimulated insulin release by pancreatic beta cells, depending on the glucose concentrations to which they are exposed.[26] It is not known whether metformin has the same effects on fetal beta cells, but if it does, metformin could attenuate fetal hyperinsulinemia from inadequate maternal glycemic control and the contribution of fetal hyperinsulinemia to macrosomia. Additionally, metformin alters the gut microbiota, which could modify offspring gut serotonin levels, fatty acid synthesis, and neurobehavioral development.[27]

Prenatal exposure of mice to metformin, at doses achieving similar concentrations to human beings, resulted in smaller birthweights compared to nonexposed mice. Subsequently, metformin-exposed offspring fed a Western-style diet post-weaning had higher weight gain, more mesenteric fat, and hepatomegaly.[28] Strikingly, the males exposed to metformin later developed impaired glucose tolerance and fasting hyperglycemia. In a second mouse model, offspring exposed to maternal metformin had higher levels of hepatic nuclear factor 4 expression, a transcription factor that activates the gluconeogenic program and controls hepatocyte differentiation.[29] The epigenetic effects of metformin could result in adverse hepatic function and metabolism. The observation that the mice were born at a lower birthweight but then had higher weight gain postnatally with consumption of a Western-style diet is of clinical concern given the increased risk in some cohorts for higher body mass index (BMI) during childhood (when eating an ad lib diet) in offspring of women treated with metformin during pregnancy.[6,7,30] The effects of metformin on the gluconeogenic program in association with hepatomegaly in mice are also concerns because of the high risk of nonalcoholic fatty liver disease in obese children, which is the leading cause of liver transplant.[31,32] Interestingly, newborns from obese GDM women already have 68% more intrahepatic fat by Magnetic Resonance Imaging/Magnetic Resonance Spectroscopy (MRI/MRS) spectroscopy than newborns from normal-weight mothers,[33] which might serve as a "first hit" to increase their risk for developing nonalcoholic fatty liver disease. We recognize that metformin may also have some beneficial effects, specifically by reducing antiangiogenic factors and possibly preventing preeclampsia, at least in some studies.[8,34] However, the risks of metformin in utero may outweigh the potential benefit to reduce preeclampsia if metformin has long-term effects on metabolic health of the offspring.

Some recent clinical studies are congruent with animal findings and it is not clear that metformin alone is effective. The Metformin in Gestational Diabetes (MiG) trial demonstrated that mothers randomized to metformin (46% of whom also received insulin to achieve glycemic targets), vs insulin alone, had less weight gain and gestational hypertension, but preterm births were increased.[35] At 2 years of age,[36] they demonstrated evidence of higher subcutaneous fat mass without evidence of a decrease in visceral fat.[37] Shortly after the SMFM statement release, the MiG investigators reported longer term outcomes from a subset of offspring at 7 years (60% of Adelaide, Australia subgroup) and 9 years of age (25% of Auckland, New Zealand subgroup), which were

analyzed separately.[7] The offspring in the MiG index trial as a whole showed no differences in rates of large-for-gestational age (LGA), although when stratified into Adelaide and Auckland subgroups, the metformin-exposed offspring from Adelaide demonstrated a statistically significant higher rate of LGA compared to insulin alone (20.7 vs 5.9%) and maternal fasting glucoses were higher compared to those exposed to insulin alone. However, at 7 years of age, there were no differences in offspring weight or body composition among the Adelaide subgroup. In contrast, the Auckland subgroup, despite showing no difference in LGA rates at birth compared to insulin, did demonstrate that at 9 years they were heavier; had higher arm and waist circumference and waist:height ratio (<0.05); and trended toward a higher BMI, triceps skinfold, and abdominal fat volume by MRI (all $P = .05$). There were no differences in glucose, lipids, insulin resistance, or liver function test measures in the metformin-exposed offspring compared to insulin from either subgroup. Interpretation of these results are complicated by the fact that only a subset of the offspring had long-term follow-up. It is unclear whether the increase in childhood weight in the Auckland group exposed to metformin that was not seen in the Adelaide group might be explained by differences in size at birth, maternal mean glucoses, BMI, gestational weight gain, ethnicity (predominantly European Caucasian in Adelaide and more mixed in Auckland), preterm birth rates, and/or total metformin exposure (timing, dosing, or duration). Nonetheless, the increased size and fat mass in the 9-year-old children from the Auckland subgroup exposed to Metformin in utero should give pause to any general recommendation for use of metformin to treat GDM.

Several studies have examined offspring of women with PCOS treated with metformin during pregnancy. Although no differences in LGA or GDM rates were found in mothers randomized to metformin vs placebo, their offspring weighed more at 1 year of age.[30,38] Among the 25 offspring followed at 8 years of age, higher fasting glucoses and systolic BPs were seen in the metformin-exposed group, despite insignificant differences in growth or body composition.[39] Another recently published follow-up study from offspring of women with PCOS who were randomized to metformin or placebo demonstrated that antenatal exposure to metformin resulted in higher offspring weight and BMI z-scores at 4 years of age, with twice as many overweight and obese children in the metformin-exposed group.[6] Taken together, the 9-year MiG offspring follow-up from women treated with metformin for GDM and the 4-year offspring follow-up from women treated with metformin for PCOS raise concerns that use of metformin in pregnancies could increase the risk of later childhood obesity. When combined with data from studies that demonstrate that early metformin treatment of women with PCOS or obesity did not prevent GDM,[34,40] these early observations raise the concern of potential long-term harm without evident short-term benefit. Moreover, the increased risk for childhood obesity among offspring of some mothers with PCOS and GDM *are consistent with fetal developmental programming by metformin, which may place the exposed offspring at later risk for metabolic disease, especially when exposed to an obesogenic postnatal environment.* Treatment of mild GDM with dietary therapy and insulin alone as needed has been associated with short-term maternal and neonatal benefits, but follow-up studies have not demonstrated a reduction in risk for childhood obesity.[41,42] It is therefore imperative that any treatments used during pregnancy have appropriate long-term follow-up to ensure that the medications themselves do not contribute to long-term metabolic dysfunction, regardless of whether the offspring appear average for gestational age or have normal fat mass at birth.

The SMFM statement reported there were "no significant differences in glycemic control or perinatal outcomes," in the MiG RCT, which is accurate, and 54% in the metformin arm achieved glucose control without supplemental insulin.[35] *However, in 46% of mothers, the trial compared metformin plus insulin to insulin alone.* The MiG offspring follow-up study demonstrated that among the Auckland subgroup, insulin had to be added to metformin in 51% of the subjects to achieve similar glycemic control as insulin alone. In the Adelaide subgroup, insulin was added to metformin in 31% of subjects, however, this did not achieve equivalent glycemic control as insulin alone.[7,35] It is also important to note in the trial that metformin alone was associated with increased maternal triglycerides compared to insulin.[35] Triglycerides and free fatty acids, resulting from their hydrolysis, are an increasingly recognized substrate for fetal fat accretion.[43,44] In fact, maternal triglycerides in the MiG study correlated with LGA and infant adiposity despite lower maternal gestational weight gain.[45–48] Although metformin would be expected to improve maternal insulin sensitivity and prevent GDM, there were no differences in LGA rate or prevention of GDM in the metformin arm of the Metformin in Obese Pregnancy or Efficacy of Metformin in Pregnant Obese Women, a Randomised Controlled Trial (EMPOWaR) RCTs, while compliance was a concern in the latter.[40,49] It is reassuring that there were no differences in rates of small for gestational age in the MiG, EMPOWaR, or Metformin in Obese pregnancy studies.[35,40,49] However, there are multiple metabolic factors that may play a role in long-term programming, particularly if the in utero environment is characterized by nutrient restriction and the postnatal environment is characterized by nutrient excess. *Given the paucity of data demonstrating that metformin alone improves maternal glycemia or prevents LGA or excess infant adiposity, it is clinically imperative that attention should be appropriately placed on the long-term risk of adverse metabolic outcomes.*

Data demonstrating that metformin is superior to glyburide are limited, and glyburide is often inappropriately administered

Although the SMFM endorsed superior safety and efficacy of metformin over glyburide, there are concerns about suboptimal dosing of glyburide in clinical studies. Glyburide is

metabolized by the liver and effluxed from the fetal to the maternal compartment against a concentration gradient by placental breast cancer resistance protein,[50] so that fetal concentrations of glyburide are less than maternal. However, recent data suggest glyburide may increase placental Glucose Transporter 1 (GLUT1) expression, potentially increasing glucose delivery.[51] Intention-to-treat analyses suggest that fetal outcomes may be less favorable with glyburide compared to metformin (often used with insulin), but this may partially be due to glyburide not being dosed according to its pharmacokinetic properties. Often unrecognized is that glyburide's peak is at 2−3 hours and the peak of insulin stimulated by glyburide is 3−4 hours after administration.[52] Therefore, glyburide's effect is much greater if given 1 hour before meals. In fact, its 3− to 4-hour peak is similar to regular insulin, supporting that glyburide should not be administered before bedtime to treat fasting hyperglycemia.[52,53] *Taking glyburide immediately before a meal or at bedtime, which is a common clinical practice,*[51,52] *is likely to result in significant maternal hypoglycemia 3−4 hours later and inability to effectively up-titrate the dose. This can result in inadequately treated 1-hour postprandial hyperglycemia, fetal hyperinsulinemia, excess fetal growth, and neonatal hypoglycemia.* It has been shown that lower blood levels are achieved in pregnancy compared to nonpregnant individuals, raising questions about insufficient dosing,[52] but irrespective of this, intention-to-treat analyses are important.

There is also a paucity of randomized clinical trials directly comparing glyburide to metformin, and all previous studies were limited by small sample sizes.[54−56] Several meta-analyses have been performed in an attempt to guide practice. Balsells et al[46] found that metformin was associated with less maternal weight gain, lower birthweight, less macrosomia, and less LGA, but preterm birth was increased in women who were treated with metformin. Another meta-analysis that used a network approach suggested that metformin has the highest probability of being the most effective treatment when compared with insulin or glyburide.[47] However, a Cochrane meta-analysis concluded that the evidence comparing insulin with oral agents was low to moderate quality and the choice may be influenced by physician or maternal preference, availability, or severity of GDM.[57,58] Much attention is placed on fetal overgrowth in the setting of GDM, but preterm birth (including late preterm birth) is also associated with long-term health consequences including adverse neurodevelopmental outcomes,[59,60] making it difficult to assess the long-term implications of one outcome over another when selecting among oral agents with limited long-term follow-up data. A recent RCT that used metformin, glyburide (often for fasting hyperglycemia), or both concluded that using both drugs reduced the need for insulin from 32−11%, and that metformin might be superior, despite metformin failing glycemic optimization more often.[61−63] Although the authors advocated for their combined efficacy, prescribing 2 drugs that cross the placenta to avoid insulin raises significant concerns.

Individualizing therapy is warranted until sufficient long-term follow-up is available

We concur with both the American Diabetes Association and American Congress of Obstetricians and Gynecologists recommendations that insulin is the preferred treatment of GDM.[64,65] A number of us have found that even a brief counseling session about the knowledge that oral agents cross the placenta and that the long-term impacts of this are unclear will result in many women choosing insulin. We acknowledge that many medications that are commonly used during pregnancy cross the placenta with limited long-term follow-up data, but we stress that GDM presents a unique scenario because of the availability of insulin, which does not appreciably cross the placenta. For patients unwilling or unable to use multiple insulin injections, we propose that the patient's individual glucose profile, fetal growth, and risks should be carefully considered rather than recommending one oral agent over the other in all patients. Patients with primarily fasting hyperglycemia (frequent in Hispanic Americans)[66] may benefit from a single dose of NPH insulin immediately before bedtime. If postprandial hyperglycemia warrants treatment and there are barriers to using multiple injections, glyburide given 1 hour before breakfast and dinner may successfully lower the 2-hour postprandial glucose. The combination of NPH at night and glyburide preprandially deserves further study.

Metformin might be particularly useful in women unwilling to use insulin or extremely fearful of hypoglycemia. Metformin does have beneficial effects in nonpregnant adults with prediabetes, type 2 diabetes, and cancer, and its effects on angiogenesis may be favorable to prevent preeclampsia. However, the same antiproliferative, mitochondrial suppressive, and hepatocellular effects cannot be assumed to be favorable in a fetus. Indeed, the recent follow-up data cited above raise concerns about the risk for childhood obesity. We applaud the investigators of the MiG and PCOS RCTs for their recent follow-up offspring studies. The same follow-up should be strongly advocated with glyburide given its potential to stimulate the fetal pancreatic beta cell and potentially, promote beta cell fatigue over the long-term.

In summary, there are both pharmacologic and randomized trial evidence that metformin may create an atypical intrauterine environment, placing exposed fetuses at risk for developmental programming and lifetime alterations that may promote an obesogenic phenotype, especially when exposed to a postnatal environment of nutritional excess.[67,68] We believe it is premature to embrace metformin as equivalent to insulin or as superior to glyburide, and that patients should be counseled on the limited long-term safety data and potential for adverse childhood metabolic effects. Carefully controlled studies that appropriately target the use of oral agents according to individual patterns of hyperglycemia and that optimize dosing according to their pharmacodynamic and pharmacokinetic properties are essential. Even more pressing are long-term follow-up studies of offspring metabolic risk in childhood and into adulthood. ■

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ABSTRACT

A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes

Use of oral agents to treat gestational diabetes mellitus remains controversial. Recent recommendations from the Society for Maternal-Fetal Medicine assert that metformin may be a safe first-line alternative to insulin for gestational diabetes mellitus treatment and preferable to glyburide. However, several issues should give pause to the widespread adoption of metformin use during pregnancy. Fetal concentrations of metformin are equal to maternal, and metformin can inhibit growth, suppress mitochondrial respiration, have epigenetic modifications on gene expression, mimic fetal nutrient restriction, and alter postnatal gluconeogenic responses. Because both the placenta and fetus express metformin transporters and exhibit high mitochondrial activity, these properties raise important questions about developmental programming of metabolic disease in offspring. Animal studies have demonstrated that prenatal metformin exposure results in adverse long-term outcomes on body weight and metabolism. Two recent clinical randomized controlled trials in women with gestational diabetes mellitus or polycystic ovary syndrome provide evidence that metformin exposure in utero may produce a metabolic phenotype that increases childhood weight or obesity. These developmental programming effects challenge the conclusion that metformin is equivalent to insulin. Although the Society for Maternal-Fetal Medicine statement endorsed metformin over glyburide if oral agents are used, there are few studies directly comparing the 2 agents and it is not clear that metformin alone is superior to glyburide. Moreover, it should be noted that prior clinical studies have dosed glyburide in a manner inconsistent with its pharmacokinetic properties, resulting in poor glycemic control and high rates of maternal hypoglycemia. We concur with the American Diabetes Association and American Congress of Obstetricians and Gynecologists, which recommend insulin as the preferred agent, but we believe that it is premature to embrace metformin as equivalent to insulin or superior to glyburide. Due to the uncertainty of the long-term metabolic risks of either metformin or glyburide, we call for carefully controlled studies that optimize oral medication dosing according to their pharmacodynamic and pharmacokinetic properties in pregnancy, appropriately target medications based on individual patterns of hyperglycemia, and follow the offspring long-term for metabolic risk.

Key words: diabetes in pregnancy, glyburide, guidelines, metformin