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EDITORIAL

Long-term effects of metformin use in gestational diabetes mellitus on offspring health

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Abstract

Metformin is the first-line drug for the treatment of type 2 diabetes mellitus, but its role in gestational diabetes mellitus (GDM) management is not clear. Recent evidence suggests a certain beneficial effect of metformin in the treatment of GDM, but a high treatment failure rate leads to the initiation of additional medications, such as insulin. Moreover, since metformin crosses the placental barrier and reaches a significant level in the fetus, it is likely to influence the fetal metabolic milieu. The evidence indicates the long-term safety in children exposed to metformin in utero except for mild adverse anthropometric profiles. Diligent follow-up of metformin-exposed offspring is warranted from the clinician's point of view.

Key Words: Anthropometry; Fetal; Gestational diabetes mellitus; Long-term; Metformin; Offspring

Core Tip: The use of metformin in mild-to-moderate gestational diabetes mellitus may confer certain advantages. Since metformin reaches almost a similar serum level in the fetus, it is likely to influence the fetal metabolic environment. Limited long-term data suggest that metformin-exposed children have mild adverse anthropometric profiles. However, the clinical significance and effect on cardiometabolic health have yet to be determined.

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INTRODUCTION

Metformin is a biguanide compound used as a first-line drug for the treatment of type 2 diabetes mellitus. However, the use of metformin in gestational diabetes mellitus (GDM) is still debated. Currently, the American Diabetes Association does not recommend metformin as a first-line therapy in GDM patients, mainly due to the absence of long-term safety data of metformin exposure in utero, and many patients additionally require insulin for the control of glycemia[1]. However, the National Institute for Health and Care Excellence Guideline of the United Kingdom recommends the use of metformin in GDM patients when diet and exercise for 1-2 wk alone fail to control hyperglycemia[2]. This is particularly recommended when fasting plasma glucose (FPG) is less than 126 mg/dL (7 mmol/L). Of note, this guideline mentions the use of metformin as off-label. This guideline also recommends using insulin with or without metformin in GDM mothers in whom FPG is greater than 126 mg/dL (7 mmol/L).

Metformin predominantly acts by decreasing hepatic glucose output by decreasing gluconeogenesis. The principal molecular mechanisms responsible are activation of adenosine monophosphate-dependent kinase and inhibition of complex I of the respiratory chain in mitochondria[3]. However, it was recently shown that metformin also decreases glycerol- and lactate-dependent gluconeogenesis by inhibiting glycerol-3-phosphate dehydrogenase enzyme[3]. Additionally, metformin acts through the intestine by modulating the gut microbiome[4], increasing glucagon-like peptide 1 secretion[5] and altering bile acid metabolism[6].

The proposed rationale of the use of metformin in patients with GDM, gestational obesity and pregnancy with polycystic ovary syndrome (PCOS) lies in its beneficial effects demonstrated in several clinical trials. Metformin was found to result in similar neonatal outcomes as insulin in GDM patients without any increase in serious adverse events in earlier studies[7,8]. More women preferred metformin over insulin during clinical trials. A recently concluded large randomized controlled trial (RCT)[9] (MiTy trial) showed multiple benefits of metformin treatment compared to placebo in GDM patients. The metformin-treated group had better glycemic control with reduced insulin requirements and less weight gain of the mother during pregnancy. Moreover, metformin-exposed infants were lighter with lower adiposity and a higher risk of being small for gestational age. A previous meta-analysis[8] reported that metformin treatment was associated with a decreased risk of neonatal hypoglycemia and large for gestational age newborns with less weight gain of the mother during pregnancy. Furthermore, metformin treatment was not associated with an increased risk of preterm delivery, perinatal mortality, small for gestational age infants, and cesarean section. Thus, it is possible that metformin might play a role in the management of GDM, gestational obesity, and pregnant women with PCOS.

There is evidence that metformin crosses the placental barrier and reaches a similar serum level in the fetus as in the mother[10], thus implying its role in the modification of the metabolic milieu of the offspring. Thus, long-term data on offspring outcomes remain an important consideration before choosing metformin for use during pregnancy. Hence, we provide a short summary and discuss future needs in this context.

LONG-TERM EFFECTS OF METFORMIN ON OFFSPRING OF MOTHERS WITH GESTATIONAL DIABETES

Effect on anthropometry and metabolic parameters of offspring

The metformin in a gestational diabetes follow-up (MiG-TOFU) cohort provided invaluable insights into offspring health[11]. The first 2-year follow-up data showed that children exposed to metformin during pregnancy had higher subcutaneous fat measurements as measured by mid-upper arm circumferences, biceps and subscapular skinfold thickness. However, they had similar total fat mass and percentage of body fat as measured by bioimpedance analysis and dual-energy X-ray absorptiometry

when compared to the insulin-exposed counterparts, as shown in Table 1. Although an ethnic difference in the prevalence of higher visceral adiposity was suggested, particularly in Indian boys at the 2-year follow-up of the MiG cohort[12], the specific effect of metformin is not known at present. The MiG cohort study was further extended to 7 years in the Adelaide cohort and 9 years in the Auckland cohort[13]. In the Adelaide cohort, there was no difference in outcomes in the offspring between the metformin and insulin treatment groups. However, the metformin-exposed group in the Auckland cohort had significantly higher weight, arm circumference, waist circumference (WC), and waist-to-height ratio. The abdominal fat components, including visceral adipose tissue, subcutaneous adipose tissue and liver fat measured by magnetic resonance imaging, were similar in the metformin group as the insulin-exposed group[13]. However, there was a trend toward a higher fat mass per volume in the metformin-exposed group. Different metabolic parameters were also found to be similar between the two groups (FPG, glycosylated hemoglobin, triglyceride, cholesterol, insulin, liver enzymes, leptin, adiponectin and biochemical markers of insulin resistance). Whether this finding is explained by the higher body mass index (BMI) of the mothers randomized to the metformin arm at the time of recruitment or the decreased nutritional intake during the later part of pregnancy is not clear.

Ijäs *et al*[14] reported a higher body weight at 12 mo and higher height and body weight at 18 mo in metformin-exposed offspring than in insulin-exposed offspring. Metformin exposure and pre-pregnancy BMI of the mother were identified as predictors of higher body weight at 18 mo during the follow-up of the offspring. However, the BMI and the percentage of overweight and obese children were not different between these two treatment groups. This study did not report any difference in terms of subcutaneous or visceral adiposity. Another observational study performed in school children from New Zealand did not find any difference in weight-for-height z-scores in the offspring of metformin- *vs* insulin-treated GDM mothers[15]. This study also did not find any difference in terms of the likelihood of having a weight for height percentile greater than the 85th percentile in the children of metformin-exposed mothers as compared to insulin treated counterparts. A recent study from India reported nine years of follow-up data of the offspring of mothers who were randomized either to metformin or glibenclamide during their GDM management[16]. They found no difference in BMI, WC or visceral fat distribution between the treatment groups. All metabolic parameters were comparable between the two groups except for a mild increase in the triglyceride levels in the metformin group. Similarly, there was no difference in the mean systolic or diastolic blood pressure (BP) among the offspring of metformin- or insulin-treated mothers in the MiG trial at the median follow-up of 29 mo of age[17].

A meta-analysis[18] performed on 684 children concluded that metformin-exposed children were heavier [standardized mean difference 0.26, 95%CI (0.11–0.4)] (heterogeneity $I^2 = 0\%$)]. Other measurements, such as body composition and height, were not different in the metformin-exposed group compared to those in the insulin/placebo group. The heavier weight of offspring during follow-up in the metformin-exposed group may reflect the effect of lower birth weight. Indeed, a recent meta-analysis has shown that metformin-exposed neonates were lighter than both glibenclamide- and insulin-exposed neonates[19]. There is evidence from animal studies that metformin-exposed offspring are born lighter and later gain more weight when fed high-fat diets [20].

Effect on other offspring parameters

Apart from anthropometric data, few studies have explored other aspects of long-term health in the offspring of metformin-exposed mothers. The psychosocial and behavioral indices were similar between the treatment groups in the study by Landi *et al*[15]. Wouldes *et al*[21] found no difference in terms of neurodevelopmental skills between the groups at the two-year follow-up of the MiG trial. Another study examined the testicular size of offspring born to either metformin- or insulin-treated GDM mothers[22]. They did not find any difference in testicular size measured by orchidometer or testicular ultrasound at the mean age of 60 mo. However, the sample size was small, and it would be interesting to note the difference in testicular size and resultant impact on gonadal function and fertility after the onset of puberty rather than at five years of age.

Long-term effect of metformin on offspring in reference to mothers with gestational obesity and PCOS

The other two clinical conditions where metformin can be used during pregnancy are

Table 1 Summary of the selected studies on the long-term effect of metformin on the anthropometry and metabolic parameters of the offspring

Ref.	Year	Country	Follow-up timing	Main outcomes
Rowan *et al*[11]	2011	Australia and New Zealand	2 yr	Metformin exposed children had (1) Larger mid-upper arm circumferences, biceps and subscapular skinfold thickness; and (2) Total fat mass and percentage body fat were similar to insulin group
Rowan *et al*[13]	2018	Australia and New Zealand	7 yr and 9 yr in Adelaide and Auckland cohort respectively	No difference in the metformin-exposed children and insulin-treated mothers in Adelaide cohort. In Auckland cohort: (1) Metformin-exposed children had larger weight, arm and waist circumferences, and waist: Height ratio; (2) Similar body fat percentage between two treatment groups; and (3) Visceral adipose tissue, abdominal subcutaneous adipose tissue and liver fat were similar in metformin exposed group in comparison to insulin treatment
Ijäs *et al*[14]	2014	Finland	mo	(1) Children exposed to metformin were significantly heavier at the age of 12 mo; and (2) Metformin exposed offspring were taller and heavier at the age of 18 mo
Landi *et al*[15]	2019	New Zealand	4 yr	No significant differences in weight, weight for height, or body mass index in children of insulin versus metformin exposed mothers
Paul *et al*[16]	2020	India	9 yr	(1) No difference in weight, body mass index, waist circumference, body fat percentages in between metformin and glibenclamide exposed children; and (2) Similar metabolic profile between two groups except mild elevation of serum triglyceride in the metformin group

gestational obesity and PCOS. However, the data regarding the long-term outcome in such settings are very sparse[23-27]. A recently concluded obese pregnant woman offspring follow-up study (77 metformin-exposed children aged 3.9 ± 1.0 years) noted similar peripheral arterial BP, arterial stiffness, and metabolic parameters (lipid profile, leptin and adiponectin) between the metformin and placebo groups[23]. The body composition was similar between the two groups except for lower gluteal and triceps circumferences in the metformin group. Interestingly, metformin-exposed children showed lower central cardiovascular hemodynamic indices and diastolic indices. Further insight into the long-term outcome associated with metformin use in women with gestational obesity will be possible when the follow-up data of two important RCTs become available (EMPOWaR and GRoW trials) in the future.

The other context is the use of metformin for PCOS. A small follow-up study did not find any difference in body composition between metformin- and placebo-exposed children at 8 years of age, but a higher FPG and systolic BP were noted in the metformin group[24]. In one of the longest follow-up RCTs, it was found that markers of obesity, such as BMI, BMI-z scores, waist-to-height ratio, and WC, were higher in metformin-exposed children than in the children in the placebo group[25]. The obese phenotype was evident by the age of 4 years (67% metformin-exposed children were either overweight or obese by 4 years of age). However, the biochemical measures of metabolic syndrome, which usually develops later in life, were similar between the groups. Combined follow-up of this RCT and its pilot study also showed similar trends of increased BMI and overweight/obese percentage among metformin-exposed children born from a PCOS pregnancy[26]. However, metformin exposure does not affect the cognitive outcome in children born to mothers with PCOS[27]. Thus, it is evident that even in the context of gestational obesity and PCOS, metformin exposure alters both anthropometric and metabolic profiles of the offspring.

CONCLUSION

To date, the evidence has indicated the long-term safety of exposure to metformin in utero except for mild adverse metabolic profiles. However, the data are limited in quantity and quality. Several questions remain to be clarified further about the long-term safety in offspring exposed to metformin in utero. First, there were not enough studies reporting long-term data. Moreover, long-term studies are prone to high dropout rates. Second, the impact of alterations in anthropometric data on cardiometabolic outcomes must be determined further in future studies. Third, whether the effect of metformin will continue until adulthood is an important point to explore. Fourth, whether metformin has a differential impact on offspring health based on ethnicity, particularly in low-income countries, needs to be explored in the future. Finally, further basic research is needed to identify and characterize the incongruity between animal studies and human follow-up study outcomes.

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