The diversity of gestational diabetes: a therapeutic challenge

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Abstract
Metformin as the first drug of choice for glucose lowering in gestational diabetes (GDM) is still controversial, despite recent publications reporting similar outcomes in comparison to insulin, both for offspring and mothers. The use of metformin during pregnancy is increasing and several recent guidelines recommend metformin use in GDM pregnancies. Background, current metformin use and unresolved concerns are discussed in the context of the article from Gante and coworkers.

Metformin and GDM have similarities, with dominating insulin resistance, family history of diabetes and variable degrees of beta cell failure (10, 11). Most women with GDM will have close-to-normal glucose levels until mid-pregnancy and become diagnosed in gestational week 24–28. At this time in pregnancy, insulin resistance and β-cell failure usually are more pronounced (12) and therefore, the need for antihyperglycemic therapy is greater. The women who are diagnosed with GDM in early gestation, i.e. before typical time for OGTT testing, are usually considered as more glucose intolerant than those with onset at gestational week 24–28 or later (13). The influence of overweight in women with GDM varies, but women with high BMI before pregnancy are overrepresented in most GDM cohorts (14, 15). Both MODY and type 1 diabetes may become manifest during pregnancy (16), which adds to the complexity of diagnosing and treating hyperglycemia in pregnancy.

Long-term data of metformin effects on the offspring are sparse, despite decades of use. The unanswered questions now are mainly related to late offspring development, growth and fertility, as well as fat mass distribution and hypothetical effects on fetal programming (17, 18). The recent years have yielded important information regarding gestational and perinatal outcomes of metformin treatment (1, 2). The results in the current
paper by Gantes and coworkers (19) are in line with previous publications. Their data are from the Portuguese Gestational Diabetes registry, describing pregnancy outcomes in 388 metformin-treated women from the total registry number of 5352 women with GDM in 2014–2015. The registry participants seem to be representative for the GDM population in Portugal, as 60% of all diagnosed with GDM during the years 2014–2015 were included. The cohort studied was fairly old and more than 40% had a first trimester GDM diagnosis. In brief, the women who did not reach the therapeutic goals during metformin treatment and therefore needed supplementary insulin treatment were older, more overweight and in the need for antidiabetic medication earlier in pregnancy than those that achieved the glycemic targets. Pregnancy outcomes were similar between the groups except a higher rate of caesarean sections and elevated glucose levels 6–8 weeks after delivery. These outcomes in this group most probably reflect a higher degree of β-cell failure, and thus, less effect of the baseline treatment.

**Metformin, effects in general**

Metformin was first marketed as an antidiabetic medication in 1957. The main mechanism of action is reduction of hepatic glucose production; however, several other antidiabetic effects may contribute, including modulation of appetite, modulation of steroidogenesis and AMP kinase activation and effects on the gut microbiota as reviewed in (17, 18, 20). Also, metformin influences vitamin B12 absorption (21), resulting in a 10–30% reduction of cobalamine levels in general diabetic therapy. Although this rarely results in anemia, it may still be important, also in pregnancy. Early embryonic tissue seems unresponsive to metformin effects, probably due to low numbers of organic cationic transporters (22) and this might explain why teratogenic effects of metformin have not been seen. The compound does cross the placenta and has been measured in cord blood at a concentration range similar to that in maternal blood (23). There has also been some concern that a reduction of placental insulin resistance during metformin treatment could influence nutrient transport to the fetus negatively during maternal fast and result in deficient fetal growth (18).

Two direct effects of metformin are inhibition of respiratory chain activity in the mitochondria and AMP kinase activation. Both these pathways have potential to influence the growing fetus, as they are highly used by proliferating tissues and hormone-producing cells (17, 18). AMP kinase is involved in meiotic processes and the regulation of transcription in environmental stresses via histone phosphorylation or acetylation. In murine studies, such activation has resulted in increased body weight and fat content in liver and mesenterium (24), possibly paralleling the findings of the Barker hypothesis (25).

Another concern has been incidents of lactacidosis during metformin treatment, currently found in 5/100 000 patients treated for T2D (26). In general, the additive effect of pronounced hypoxia and hypoperfusion must be present if metformin shall provoke lactacidosis, in contrast to phenformin that has higher affinity for mitochondrial membranes and therefore is more prone to result in this potentially dangerous side effect (27).

**Effects of metformin therapy early in pregnancy**

The early use of metformin (i.e. preconceptionally and in first and second trimesters) has mainly been investigated in studies of women with PCOS. These women have increased risk of GDM, but metformin treatment reduced their GDM risk by at least 10% (28, 29). The ameliorating influence of metformin on metabolism and fertility seems related to BMI and excess fat mass. Obesity (e.g. BMI ≥ 30 kg/m²), long duration of infertility or major hyperandrogenism seem to result in resistance to the beneficial effects of metformin treatment (30).

The outcomes of studies of metformin on women with PCOS diverge, probably due to varying duration and initiation of therapy for PCOS, different PCOS criteria and treatment goals (ovulation, conception or live births) and also different infertility treatments or diverging BMI in the groups. This hampers the interpretation of these results, however, malformations or teratogenicity, preconceptionally or in pregnancy, are not increased (31, 32). Recent data show that 258 PCOS women treated with metformin increased less in weight during pregnancy than placebo subjects, but had increased insulin resistance and less weight loss 12 months postnatally (n=199, questionnaire based) (33). Neonates of the overweight or obese women in this study had significantly larger head circumference (34), and the whole infant group weighed on average 500g more at one year of age compared to infants in the placebo group (33).
Studies of metformin therapy in GDM

An early study of 63 women with GDM, who failed treatment goals with lifestyle intervention only and were randomized to metformin or insulin, demonstrated similar glucose levels and pregnancy outcomes between the treatment groups (35). There was no treatment failure in the metformin group, and the majority had good glucose control on low metformin doses. In the landmark study, Metformin in Gestational diabetes (MIG), 751 women with GDM were randomized in week 20–33 to treatment with metformin or insulin (36). Of the 363 women that were given metformin, 92% continued this treatment, but 46% needed additional insulin treatment. No differences in pregnancy outcomes or serious adverse events were found between the metformin and insulin groups, and a majority of the women would have preferred the same treatment again. In the same study, maternal and cord blood lipids, glucose and CRP levels were comparable between treatment groups (37). The strongest predictors of birth weight >90 percentile were maternal triglycerides and measures of blood glucose control at gestational week 36 (37). In a follow-up study, no adverse effects on neurological development was detected in Finnish children born to mothers that had received metformin in pregnancy and who were followed up until the age of 18 months (38).

Later studies of metformin use in GDM

After the MIG study, metformin has been used in pregnancy with increasing prevalence. In a non-randomized, observational study from Australia (39), women with GDM were free to choose between treatment options: lifestyle intervention (n=371), insulin (n=399) or metformin (465 of whom 216 subsequently also received insulin). Those that were treated with anti-diabetic medication had significantly higher BMI and fasting glucose levels at diagnosis than those that had lifestyle intervention only. Pregnancy outcomes were similar between diet- and metformin-treated women. The rate of caesarean sections were significantly increased in the insulin-treated women, as were the rate of premature deliveries, macrosomia, use of neonatal intensive care units and neonatal hypoglycaemia. Fewer adverse events were seen with metformin use than with insulin treatment, but baseline differences between the groups could have influenced these results. Several other small studies show similar results and taken together, it seems like insulin treatment in addition to metformin is needed in 15–20% of GDM women.

Unsettled metformin effects

Recent insight in the potential beneficial effects of metformin on cancer growth and longevity (40) has raised the question whether metformin could result in negative long-term effects on cardiometabolic outcomes via fetal or placental programming (18, 24). The follow-up results from the MIG study at 2 years (41) indicate that the metformin treatment may influence neonatal fat distribution. However, fat mass was only increased in the extremities and not viscerally, which was interpreted as beneficial. Some research groups have questioned gonadal effects of metformin, as mice exposed to the drug in utero were found to have smaller testes, smaller tubuli seminiferi diameters and fewer Sertoli cells than control mice (42). Limited human data related to testicular development exist, but at 2 years of age, similar levels of sex hormones and AMH were found in metformin-exposed infants vs control subjects, although SHBG levels were somewhat increased in the metformin-exposed boys (43). Measurement of testicular size in prepubertal boys exposed to metformin during gestation at 33–85 months of age failed to demonstrate any difference between metformin-exposed and -non-exposed children (44). It is debated whether measuring anogenital distance could give a more precise estimate of testosterone exposure in fetal life (45).

Conclusion

The results of recent observational and randomized controlled studies of GDM indicate that current knowledge and treatment strategy are not sufficient to ameliorate maternal and offspring adverse outcomes sufficiently. Thus, there is need for improved targeted interventions that have been shown to be of benefit, such as intensified treatment (14) or screening for gestational hyperglycemia in the first trimester, that is advised by some groups and guidelines (4, 13). Facilitating and improving national birth registries could also assist us in answering the unresolved points addressed here. Metformin has been used for several decades in PCOS pregnancies and was reintroduced more recently as treatment for GDM. Current knowledge indicates that it
is a cheap and effective treatment, without increased risk for malformations or teratogenicity compared to other therapeutic options (1, 2). Results from longer follow-up of previously published studies and from a new intervention study with metformin and placebo (EMERGE, NCT no. 02980276) should be available during the next 1–2 years. However, use of metformin in common GDM, in pregnancies with good fetal growth and normal maternal renal function, can be considered a cost-effective and useful treatment alternative.

Declaration of interest
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References
13 Hughes RC, Moore MP, Gullam JE, Mohamed K & Rowan J. An early pregnancy HbA1c >/=5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. Diabetes Care 2014 37 2953–2959. (https://doi.org/10.2337/dc14-1312)
18 Lindsay RS & Loeken MR. Metformin use in pregnancy: promises and uncertainties. Diabetesologia 2017 60 1612–1619. (https://doi.org/10.1007/s00125-017-4351-y)


27 Kuan W, Beavers CJ & Guglin ME. Still sour about lactic acidosis years later: role of metformin in heart failure. Heart Failure Reviews 2017 Epub. (https://doi.org/10.1007/s10741-017-9649-9)


30 Fleming R, Hopkinson Z, Wallace AM, Greer IA & Sattar N. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. Journal of Clinical Endocrinology and Metabolism 2002 87 569–574. (https://doi.org/10.1210/jcem.87.2.8261)


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