Metformin in pregnancy

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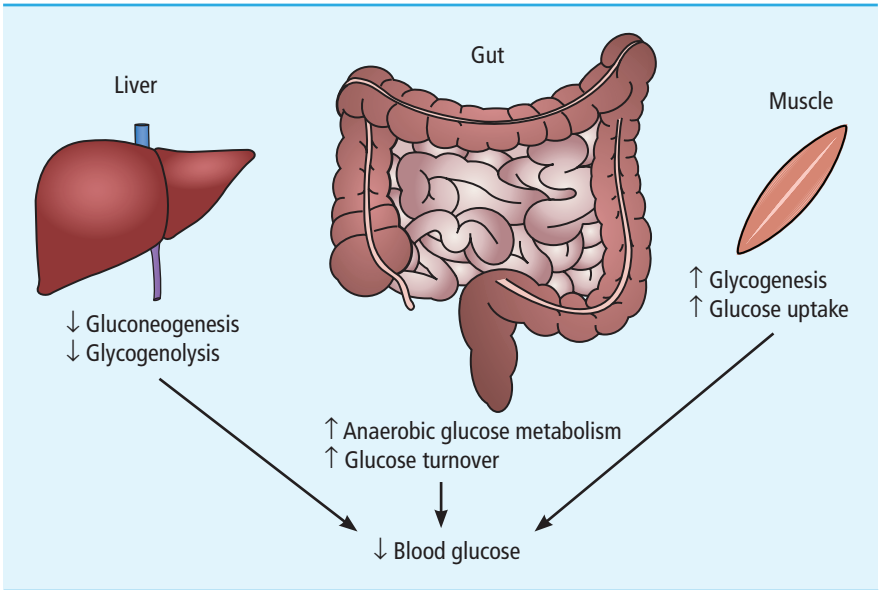

Figure 1. The pharmacological action of metformin

Introduction

Up to 5% of pregnant women in the UK have pre-existing diabetes or develop gestational diabetes (GDM). Diabetes in pregnancy is associated with increased risk of obstetric and perinatal complications, and for the mother GDM carries a long-term risk of developing type 2 diabetes mellitus (T2DM) of up to 50%. Even mild hyperglycaemia has been associated with increased rate of fetal loss in early and late pregnancy, as well as congenital defects, accelerated fetal growth and increased risks of shoulder dystocia and birth trauma. The benefits of metformin in treating T2DM, including improved cardiovascular outcomes, are well established. There may also be benefits in adding metformin to insulin-based regimens in type 2 diabetes.

The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated a clear linear relationship between maternal glycaemia and adverse perinatal outcomes, in keeping with previous evidence of the benefit of treating even mild maternal hyperglycaemia.[1] The conventional treatment for women with GDM inadequately controlled by dietary measures alone is insulin, but metformin has emerged as a safe, acceptable alternative and/or adjunct to insulin therapy and, although it does not currently have marketing authorisation for use in pregnancy, several national guidelines recommend its use in the treatment of both GDM and T2DM in pregnancy.

Pharmacology

The pharmacological action of metformin is outlined in Figure 1. Metformin inhibits hepatic gluconeogenesis, and augments glucose uptake in peripheral tissue, mainly in skeletal muscle. It also reduces the intestinal absorption of glucose and lowers serum levels of LDL and VLDL cholesterol. These effects are controlled by the phosphorylation and activation of AMP-activated protein kinase (AMPK), which suppresses gluconeogenic and lipogenic gene expression. Metformin is excreted unchanged in the urine, with a half-life of 5 hours. As glomerular filtration rate is increased in pregnancy by up to 40%, it is eliminated faster in this setting. Metformin crosses the placenta and fetal concentrations reach at least half of maternal levels, but there has been no evidence of teratogenicity in animal models, at significantly elevated drug concentrations compared to doses used in humans. Transmission of metformin to breast

milk is minimal, and NICE advises that women with pre-existing T2DM can continue to take metformin while breastfeeding.

Metformin is generally well tolerated; its main side effects are gastrointestinal, but these tend to be transient and can be attenuated by ingesting metformin with food, and using prolonged-release preparations.

Short-term outcomes of metformin in pregnancy

Several randomised controlled trials (RCTs) have demonstrated that metformin is safe and effective in treating hyperglycaemia in pregnancy, both in pre-existing and gestational diabetes, and that it may confer advantages over insulin therapy alone. The Metformin in Gestational Diabetes (MiG) trial reviewed the effectiveness and safety of metformin in the treatment of GDM and recruited 751 women who were randomly assigned to oral metformin or insulin alone.[2] Of the 363 women commenced on metformin, 46% required supplemental insulin, but at notably lower doses than women treated with insulin alone. The primary outcome was a composite of neonatal indices including prematurity; no significant difference was observed between the two groups. Individual analysis of these components revealed higher occurrence of severe neonatal hypoglycaemia in babies born to mothers on insulin alone. Secondary outcomes included maternal weight gain, which, as expected, was significantly less in those taking metformin compared to insulin. The MiG trial also found that patient acceptability of metformin was higher: 77% of women on metformin said they would choose it again in subsequent pregnancies while only 27% of those on insulin would opt to have insulin treatment again. Gastrointestinal side effects of metformin required 32 women (8.8%) to reduce their dose but only seven (1.9%) had to stop treatment.

A systematic review and meta-analysis assessed the short- and long-term maternal and fetal impact of metformin in pregnancy compared with insulin, and concluded that metformin had no short-term adverse effects on pregnancy and had potential neonatal benefits.[3] Compared with insulin, use of metformin did not significantly affect the rate of preterm delivery or Caesarean section rate, and it did not increase the risk of small for gestational age babies or macrosomia. Glycaemic control, as assessed in the third trimester or at delivery, was not significantly different in women treated with metformin from those treated with insulin. Use of metformin over insulin conferred lower risks of large for gestational age babies, neonatal hypoglycaemia and admission to neonatal intensive care units, as well as reduced rates of pregnancy-induced hypertension.

There is also evidence that use of metformin both in the pre-conception period and during pregnancy may have specific benefits for patients with polycystic ovarian syndrome (PCOS): a recent meta-analysis of studies including over 1600 women showed its association with reduced pregnancy loss and a nine-fold reduction of GDM.[4] To date, no RCTs have assessed the use of metformin in pregnant women with T2DM, but a Canadian trial is currently underway in 25 centres to assess whether metformin is a beneficial adjunct to insulin in these patients.[5]

Long-term outcomes of metformin in pregnancy

Long-term data on *in utero* exposure to metformin are limited. The MiG TOFU trial followed up over 300 children of women in the MiG trial to evaluate possible effects of metformin on body composition.[6] This showed that overall body fat at two years of age was the same in children exposed to metformin *in utero* as in those exposed to insulin alone, but that those exposed to metformin had more subcutaneous fat. This may suggest they will have less visceral fat later in life, with a potential beneficial impact on insulin sensitivity, but further research is required. Data on long-term effects of *in utero* exposure to metformin have also been acquired through the study of women with PCOS (without a diagnosis of diabetes). One small RCT of 25 pregnant women with PCOS demonstrated that those exposed to metformin *in utero* had a higher systolic blood pressure and raised fasting blood glucose at eight years of follow up.[7] Further research is required to evaluate the long-term effects of *in utero* exposure to metformin in those with or without diabetes.

Key points

- Hyperglycaemia in pregnancy is associated with an increased risk of obstetric and perinatal complications
- Metformin is considered to be a safe and effective alternative to insulin therapy and/or an adjunct to treatment both in the treatment of type 2 diabetes in pregnancy and GDM
- Long-term safety of exposure to metformin *in utero* needs further research

Discussion

Metformin appears to be a safe and effective alternative to insulin therapy and/or an adjunct to treatment both in the treatment of T2DM in pregnancy and of GDM, and has now been used in these conditions for several years. It does not appear to have any teratogenic effects, rapidly achieves good glycaemic control in many pregnancies and has no additional side effects to those associated with its use in T2DM. The therapeutic use of metformin in pregnancy confers several benefits to both mother and fetus, and its role in the management of diabetic pregnancy is now well established.

Declaration of interests

There are no conflicts of interest declared.

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