Pregnancy: Effect of metformin on pregnancy outcomes in obese women without diabetes (EMPOWaR study)

The results of a UK randomised controlled trial suggest that metformin taken by nondiabetic obese women during pregnancy has no statistically significant effect on neonatal birthweight or other maternal and neonatal secondary outcomes compared with placebo. Maternal diarrhoea and vomiting were more common with metformin. This study supports NICE guidance on weight management before, during and after pregnancy, which considered dietary and physical activity interventions. Off-label use of metformin was not included in the scope of the guideline.

Overview and current advice

NICE guidance on weight management before, during and after pregnancy advises that maternal obesity increases the risks to health for the mother and child during and after pregnancy. These include the risk of impaired glucose tolerance and gestational diabetes, miscarriage, pre-eclampsia, thromboembolism and maternal death. A relatively small gain of 1 or 2 kg/m² in body mass index (BMI) between pregnancies may increase the risk of gestational hypertension and gestational diabetes, even in women who are not overweight or obese. It also increases the likelihood of giving birth to a large baby. Babies born to obese women are also at higher risk of poor outcomes including death, stillbirth, congenital abnormality and subsequent obesity.

The prevalence of obesity in pregnant women is expected to continue to increase in parallel with the increasing trend in the general population. NICE guidance advises on the potential benefits of commissioning weight management services before, during and after pregnancy. NICE guidance recommends that management includes assessing and monitoring body weight. Health professionals should advise, encourage and help women with a BMI of 30 kg/m² or more to reduce weight before becoming pregnant and help them to achieve and maintain a healthy weight before, during and after pregnancy by eating healthily, being physically active and gradually losing weight after the baby is born.

The NICE guideline on weight management before, during and after pregnancy states that there are few well-designed UK intervention studies on weight management in pregnancy and after childbirth. In particular, there is a lack of evidence on safe, effective interventions for women who are obese but...
who do not have diabetes, and those who are breastfeeding. According to a Cochrane review protocol, use of metformin in obese pregnant women may have some potential benefits for mothers and babies because of its insulin-sensitising and antihyperglycaemic properties and there has been media interest in its use. Note that this use of metformin is off-label and the NICE guidance on weight management before, during and after pregnancy considered dietary and physical activity interventions but use of metformin was not included in the scope.

New evidence

A randomised controlled trial (RCT) has considered whether metformin reduces birthweight when given to obese women during pregnancy, based on the hypothesis that reducing maternal insulin resistance and hyperglycaemia might reduce excessive neonatal birthweight and the subsequent risk of obesity and ill health. The RCT was double-blind, placebo-controlled and recruited women from antenatal clinics at 15 NHS hospitals in the UK. Eligible women (n=449) were aged 16 years or older (mean age 29 years), with a BMI of 30 kg/m² or more (mean BMI 37.7 kg/m²) and were between 12 and 16 weeks pregnant, with normal glucose tolerance. Exclusion criteria included non-white women, concomitant systemic disease requiring treatment, those with pre-existing diabetes or gestational diabetes (either diagnosed before randomisation or in a previous pregnancy) and previous delivery of a baby smaller than the 3rd percentile for weight. Baseline demographics, medical history and maternal anthropometry (physical measurements) were similar between groups.

Participants were randomised to metformin 500 mg (n=226) or matching placebo (n=223), at a dosage of up to 5 tablets daily in 2 or 3 divided doses, starting at 12 to 16 weeks gestation and continuing until delivery. The method of randomisation used suggests allocation was concealed. Treatment started at 1 x 500mg tablet once daily and was titrated gradually over 5 weeks to reach the maximum tolerated dose or 2500 mg (whichever was lower, median dose 2000 mg). Compliance was monitored (around 66% in both groups) and women were followed up regularly throughout pregnancy, at time of delivery and at 3 months post-delivery.

The primary outcome was Z-score (a statistical measurement) corresponding to the gestational age, parity and sex-standardised birthweight percentile of liveborn babies delivered at 24 weeks or more gestation. Primary analyses were undertaken in the modified intention-to-treat (mITT) population (excluding 15 women who could not be included in analyses because of, for example, stillbirth, miscarriage or termination) and the per-protocol (PP) population, comparing outcomes amongst participants who were compliant with treatment (defined as taking at least 1 tablet for at least 4 days per week for at least half of the weeks from randomisation to delivery). Secondary outcomes included various measures of maternal biochemistry at 36 weeks gestation (including insulin resistance and glucose tolerance), and anthropometry of mothers and babies. However, the authors note that these are exploratory analyses only.

At delivery, mean birthweight did not differ between metformin (n=214, 3462 g) and placebo (n=220, 3463 g), and there was no significant difference between the groups in the primary outcome of Z-score of birthweight percentile (adjusted odds ratio [OR] =0.93, 95% confidence intervals [CI] =0.68 to 1.26, p=0.60). Furthermore, metformin had no effect on insulin resistance or glucose tolerance at 36 weeks, or prevention of gestational diabetes or maternal weight gain compared with placebo. The authors stated that this absence of effect was apparent in both the mITT and PP analyses.

Diarrhoea and vomiting were statistically significantly more common in women in the metformin group compared with the placebo group (42% and 19% respectively for diarrhoea [OR 3.11, 95% CI 1.97 to 4.91, p<0.0001], 32% and 22% respectively for vomiting [OR 1.67, 95% CI 1.06 to 2.62, p=0.03]). The incidence of other adverse outcomes were similar between the 2 treatment groups, including preterm birth, low birthweight, caesarean section, postpartum haemorrhage and the combined outcome of miscarriage, termination of pregnancy, stillbirth or neonatal death.
The authors state that the strengths of the study are the multicentre randomised controlled design, making the results robust and generalisable, and that recruitment achieved the pre-specified target, ensuring the trial was statistically powered despite compliance being lower than anticipated. The authors conclude that the failure to detect a significant effect between metformin and placebo is a strong negative finding rather than a result of the trial being underpowered.

**Commentary**

**Commentary provided by Medicines and Prescribing Programme**

According to Chiswick et al. this was a UK study of sufficient power and the results could therefore be generalisable to clinical practice. Exclusion of non-white women from the recruitment cohort could be a study limitation in terms of application. In the accompanying editorial Refuerzo acknowledges that EMPOWaR was a well-designed study and goes on to postulate that the idea that metformin administered during pregnancy could reduce birthweight in high-risk, obese pregnant women is not biologically implausible and this hypothesis is supported by a Cochrane review protocol. However, Chiswick et al. concluded that the EMPOWaR study showed a true absence of effect of metformin on birthweight rather than it being a spurious result occurring through study design error. Refuerzo suggests that metformin may have a greater effect if initiated in the peri-conceptual period instead of late in the first trimester as it was in the EMPOWaR study. For example, it is common practice to administer metformin before or near the onset of conception in women with polycystic ovary syndrome and longer lengths of treatment are required to reduce weight over time. Refuerzo postulates that poor adherence with treatment may have affected the result. Only 38% of participants in the metformin group complied with taking the highest dose of 2500 mg per day, and 62% complied with the 2000 mg per day regimen. Perhaps not enough participants took the medicine at sufficient doses to result in a significant difference in the primary outcome. Indeed, this problem might reflect ‘real world’ practice where adverse events affect compliance, particularly in pregnant women who may already have reservations of taking any treatment due to the potential risks of exposure to their unborn child.

Although the primary outcome in this study was negative, some benefit was seen in maternal secondary outcomes for women taking metformin compared with placebo, such as reductions in fasting plasma glucose and lower insulin concentrations at 28 weeks but these were not maintained at 36 weeks. Refuerzo suggests that perhaps future studies in this area should focus on the potential maternal benefits of metformin.

In the Cochrane review protocol, Eames et al report that metformin is being used increasingly in the treatment of gestational diabetes, having been shown to result in decreased rates of caesarean birth and neonatal hypoglycaemia. According to Chiswick et al, this present study provides experimental evidence that factors other than maternal glucose are important in fetal overgrowth. It is unclear if metformin will have a future beneficial effect on the risk of obesity and metabolic syndrome for the children born to mothers in the EMPOWaR study and further long term follow up of these children is planned. In the meantime, metformin should not be used off-label to improve pregnancy outcomes in obese women and health professionals should to continue to follow NICE guidance which recommends helping women to achieve and maintain a healthy weight before, during and after pregnancy by eating healthily, being physically active and gradually losing weight after the baby is born.

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References


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