Metformin Antenatal Formulations Study Pilot Study (METAFOR)

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End of Study Lay Summary

METAFOR aimed to find an effective and well-tolerated drug therapy for women and birthing people with gestational diabetes, the most common pregnancy complication.

Metformin IR (immediate release) is widely used as first-line drug therapy in the UK to control blood sugar levels. Metformin has significant advantages, including that it is a tablet and it helps limit pregnancy weight gain. However, standard metformin IR also has poorly tolerated side effects including nausea and diarrhoea. Moreover, it freely crosses the placenta to the baby. There is uncertainty about whether there could be any potential long-term effects of metformin exposure for the child. In this pilot study we aimed to test whether a new "delayed-release" (DR) metformin tablet could be a feasible and acceptable alternative for women with gestational diabetes. This tablet contains exactly the same active ingredient, which is metformin. However, the new tablet gets absorbed into the body in a lower part of the gut, rather than in the stomach. We think that this will result in fewer side effects than regular metformin tablets (metformin IR) and substantially reduced levels of metformin crossing the placenta to the baby.

The METAFOR study involved three 'arms' and aimed to recruit a total of 50 women with singleton pregnancies and gestational diabetes:

- Arm 1: Participants (women scheduled for elective Caesarean section at ≥37 weeks) were to take one metformin DR 900 mg tablet on the morning of delivery by Caesarean section with blood, umbilical cord and placenta sampling.
- Arm 2: Participants (women between ≥28 and ≤36 weeks gestation) were to take one metformin DR 900 mg tablet prior to serial blood and urine sampling at a clinical research facility.
- Arm 3: Participants (women who are adequately treated with metformin IR at <36 weeks pregnant) were to be randomly allocated to continue their own standard dose of metformin IR for 7 days, followed by 7 days of metformin DR 900 mg or vice versa.

Due to unforeseen and unavoidable delays during the initial phase of this project (largely caused by lengthy discussions regarding the drug supply agreement as well as exceptionally long Medicines and Healthcare products Regulatory Agency review timelines), the trial opened to recruitment approximately 12 months behind schedule. The original batch of study drug expired in December 2023 and we were unable to source additional study drug. Consequently, the trial had to be terminated earlier than expected after being open to recruitment for only approximately three months. During that time, 234 women were screened between two study sites, 16 women were approached and one participant was recruited to trial Arm 1. Since this trial was terminated early with n= 1 participant, there has been no formal analysis. However, the participant's blood samples appear to support our hypothesis that reduced levels of metformin DR are crossing the placenta compared to metformin IR.

While we were not able to complete the study, we have gained experience with regards to realistic set-up timelines, and have gathered important feedback from site teams on the study documentation and collected screening data. This will be valuable information for future studies.

Notes:

The terms 'women' and 'birthing people' are used in this trial's participant facing information to refer to those who are pregnant, and give birth. We acknowledge that not all people who are pregnant and give birth identify as women, and it is important that evidence-based care for maternity, perinatal and postnatal health is inclusive.

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