ISRCTN90686599 https://doi.org/10.1186/ISRCTN90686599

METAFOR: studying delayed-release metformin to control blood sugar levels for women with gestational diabetes

Submission date
09/12/2022

Recruitment status
No longer recruiting

Registration date
11/07/2023

Overall study status
Stopped

Last Edited
29/04/2024

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
We will address the unmet clinical need for an effective, well-tolerated, and safe drug therapy for women 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 and has significant advantages over other available drug therapies for women, including that it is a tablet and it helps limit pregnancy weight gain.

However, standard metformin IR has poorly tolerated side effects including nausea and diarrhoea. It also freely crosses the placenta, and emerging evidence suggests the potential for adverse child health outcomes including obesity.

We plan to perform a three-arm pilot proof-of-principle trial consisting of two non-randomised arms and one crossover randomised controlled arm involving 50 women using a new “delayed-release” (DR) metformin tablet which we hypothesise will substantially reduce levels of metformin in the mother’s blood and will reduce transfer of metformin across the placenta compared to metformin IR tablets, minimising the potential for adverse effects of metformin exposure for the child.

We also aim to assess whether this metformin DR preparation compared to metformin IR is a feasible and acceptable alternative to other drug therapy for women with gestational diabetes and will have fewer side effects, which will encourage women to take their treatment regularly, thus improving their blood sugar control and avoiding the need for insulin injections.

Our findings will support an application for a larger DR delayed-release as a treatment to optimise the management of gestational diabetes with the fewest side effects for mother and baby.

Who can participate?
Women who are pregnant and experiencing gestational diabetes.

Please note: We use the term 'women' in our participant information and protocol 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.

What does the study involve?
Please refer to the participant information sheets for this information (to be uploaded at a later date).

What are the possible benefits and risks of participating?
Benefits:
There are no immediate benefits of taking part in this study. However, the findings will be important in helping find an effective and well-tolerated treatment for gestational diabetes. If this is shown to be the case, we hope that this will benefit lots of pregnant women in the future.
Risks:
We are aware that participants in this study will give up their valuable time for participation. Other than that, the major risk and burden relates to the potential adverse effect of the IMP. Metformin treatment holds significant advantages for women but has poorly tolerated side effects and freely crosses the placenta with increasing concern regarding the potential for adverse long-term offspring health outcomes. Delayed-Release metformin (Metformin DR) is a new formulation of metformin hydrochloride designed to reduce systemic metformin exposure while retaining efficacy in maintaining normoglycaemia.
Study-specific blood tests will also be performed on all women at baseline, and as per individual sub-study protocols. Blood tests at baseline include: full blood count, kidney and liver function, random venous glucose, and HbA1C. Risk is minimised in this study by ensuring normal renal and liver function in all women prior to randomisation.
Metformin levels will also be assessed in all blood tests taken after ingestion of the IMP.

Where is the study run from?
University of Edinburgh (UK)

When is the study starting and how long is it expected to run for?
June 2022 to May 2024

Who is funding the study?
Chief Scientist Office (UK)

Who is the main contact?
Dr Anna Heye, METAFOR.trial@ed.ac.uk
Dr Rebecca Reynolds, r.reynolds@ed.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2022-001240-24

Integrated Research Application System (IRAS)
1004070

Protocol serial number
AC21117

Study information

Scientific Title
METAFOR Study Pilot: Metformin Antenatal Formulations Study Pilot: an open-label feasibility study

Acronym
METAFOR

Study objectives
Primary objectives:
In this study we aim to test whether a new “delayed-release” metformin tablet is a feasible and acceptable alternative for women with gestational diabetes. This will be a first-in-pregnancy

usage of metformin DR and we hope to see if women will be willing to take a new formulation of metformin in pregnancy.

Secondary objectives:
1. To explore acceptability and tolerability of metformin delayed-release (DR) in pregnancy
2. In studies of people who are not pregnant, the new metformin tablet has fewer side effects than regular metformin tablets. If this is the case for pregnant women, it would make it easier for women to take their treatment regularly, thus improving their blood sugar control and avoiding the need for insulin injections
3. To demonstrate that metformin DR lowers blood sugar levels in women with gestational diabetes with similar effects to metformin IR. Due to the delayed release formulation we think there will be reduced levels of metformin crossing the placenta to the baby.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/06/2023, East of England - Cambridge East Research Ethics Committee (2 Redman Place, London, EC20 1JQ, UK; Tel: not provided; CambridgeEast.REC@hra.nhs.uk), ref: 23/EE /0012

Study design
Interventional randomized cross over trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Gestational diabetes in pregnancy

Interventions
ARM 1 (Non-randomised):
Population: 20 pregnant women diagnosed with gestational diabetes with singleton pregnancies and a clinically documented plan to have birth by elective Caesarean section ≥37 weeks' gestation.
Duration of treatment phase: 24 hours
Treatment allocation: On receipt of a trial specific prescription, Pharmacy will dispense 4 Metformin DR 900mg tablets (1 to be taken by participant, 3 provided as an overage).
Dose: One Metformin DR 900mg tablet orally within 3 to 8 hours prior to planned Caesarean section
Follow Up: Delivery outcomes collected from mother and baby records at 28 days post-delivery (+/- 3 days)

ARM 2 (Non-randomised):
Population: 10 pregnant women diagnosed with gestational diabetes with singleton pregnancies between ≥28+0 and ≤36+0 weeks gestation. Only patients from the Edinburgh Royal Infirmary, NHS Lothian site will be recruited to this arm of the study. Arm 2 requires a day admission to the Clinical Research Facility Trials Unit and a single dose of metformin DR with serial blood

sampling.
Duration of treatment phase: 24 hours
Treatment allocation: On receipt of a trial specific prescription, Pharmacy will dispense 4 Metformin DR 900mg tablets (1 to be taken by participant, 3 provided as an overage).
Dose: One Metformin DR 900 mg tablet to be taken orally with or after breakfast and 1.5 hours (-1+2 hours) prior to commencement of blood sampling at clinical research facility.
Follow Up: Delivery outcomes collected from mother and baby records at 28 days post-delivery (+/- 3 days)

ARM 3 (Randomised crossover, web-based randomisation system allocated at 1:1 ratio):
Population: 20 pregnant women diagnosed with gestational diabetes with singleton pregnancies documented in the patients' medical notes to be adequately treated with metformin <36+0 weeks pregnant.
Duration of treatment phase: 2 weeks
Treatment allocation:
Once the crossover randomisation allocation has been generated, the next available IMP pack (8 Metformin DR 900mg tablets) for Arm 3 will be dispensed on receipt of a prescription (7 to be taken by participant, 1 provided as an overage). They will be randomised to:
• Continue to take their own normal standard prescribed daily dose of Metformin IR for first 7 days and then given the IMP Metformin DR 900mg tablet daily for 7 days at the follow-up visit OR
• Be given the IMP Metformin DR 900mg tablet daily for the first 7 days and at the follow up visit at 7 days advised to take their own normal standard prescribed daily dose of Metformin IR for 7 days.
Dose: One Metformin DR 900mg tablet once a day for 7 days
Follow Up: Delivery outcomes collected from mother and baby records at 28 days post-delivery (+/- 3 days)

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Metformin

Primary outcome(s)
Fetal metformin exposure measured by the maternal: fetal serum metformin ratio using paired maternal and umbilical cord blood samples at delivery by elective Caesarean section in Arm 1 up to 3 months following delivery, data extracted from record of mother and baby.

Key secondary outcome(s))
Up to 3 months following delivery, data extracted from record of mother and baby:

Arm 1:
1.1. Placental metformin level at delivery
1.2. Placental metformin transporter levels at delivery
1.3. Maternal plasma metformin level at delivery

1.4. Fetal serum metformin level at delivery
1.5. Fetal arterial:venous metformin ratio at delivery
1.6. Detection of metformin in maternal serum 24 hrs post-delivery

Arm 2:
2.1. AUC of maternal serum metformin levels in the third trimester.
2.2. Pharmacokinetic parameters of metformin in maternal blood, including peak serum concentration, half-life, bioavailability, renal clearance
2.3. Metformin concentrations in maternal urine

Arm 3:
3.1. Percentage of eligible participants recruited i.e. number who agree to take part out of all eligible participants who are approached.
3.2. Side-effects of treatment by questionnaire
3.3. Acceptability of treatment by questionnaire
3.4. Concordance with treatment by questionnaire
3.5. Percentage maternal blood glucose readings within local clinical target range
3.6. Need for additional gestational diabetes therapy at the end of 1 week of metformin DR/IR
3.7. Average plasma glucose concentration

Completion date
16/01/2024

Reason abandoned (if study stopped)
Lack of staff/facilities/resources

Eligibility

Key inclusion criteria
1. Women who are pregnant with singleton pregnancy
2. Women with a documented diagnosis of gestational diabetes in their current pregnancy EITHER/OR Women who are documented to be currently treated for gestational diabetes due to a documented history of gestational diabetes in a previous pregnancy
3. Women who are able to give written informed consent to participate

In addition:

Arm 1:
1. Planned for elective Caesarean section at ≥37 weeks gestation
2. Women with gestational diabetes documented to be treated with diet alone

Arm 2:
1. Women who are in the third trimester of pregnancy (≥28+0 weeks and ≤36+0 weeks gestation at consent)
2. Women with gestational diabetes documented to be treated with diet alone

Arm 3:
1. Women ≤36+0 weeks pregnant at randomisation
2. Women with gestational diabetes documented to be treated with diet and standard metformin IR (standard dose 1000 mg once daily or 500 mg twice daily)

Please note: We use the term 'women' on this site and in the study protocol 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. Our participant-facing study documents utilise appropriate gender-inclusive language.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Key exclusion criteria
1. Pre-existing diabetes mellitus
2. Taking glucose-lowering agents other than metformin (insulin, glibenclamide)
3. Previous delivery of a baby <3rd centile by weight or previous serious adverse pregnancy outcome (e.g. stillbirth or early neonatal death)
4. Known sensitivity to metformin hydrochloride or any of the known excipients.
5. Documented acute clinical condition at the time of study entry with the potential to alter renal function, such as dehydration sufficient to require intravenous infusion, severe infection, shock and intravascular administration of contrast agents.
6. Known diagnosis or documented clinically suspected acute or chronic diseases that may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, hepatic insufficiency, acute alcohol intoxication and alcoholism.
7. High risk of operative blood loss >1 litre at Caesarean section, e.g. placenta praevia, >2 previous Caesarean sections
8. Currently lactating
9. Known fetal anomaly
10. Multiple pregnancy
11. History of, or currently clinically suspected, liver failure or dysfunction at the time of trial entry
12. History of, or currently clinically suspected, severe renal failure or dysfunction at the time of trial entry**
13. History of, or currently clinically suspected, (any type of) acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
14. Previous known severe renal failure (GFR < 45 mL/min)**
15. Already enrolled in another randomised clinical trial involving IMP.
16. Taking prescribed drug known to affect renal function or result in haemodynamic change
17. Receiving investigation using iodinated contrast agent

In addition:
Arm 3:
18. Women who have two or more routine blood glucose values out of range at the same time

point on consecutive days, within the 14 days prior to consent, without a valid reason in the opinion of the PI.
19. Women who regularly fail to check glucose by finger prick on 2 or more times per day

Date of first enrolment
06/09/2023

Date of final enrolment
03/12/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
United Kingdom
EH16 4SA

Study participating centre
The Rosie Hospital
Addenbrookes Hospital
Robinson Way
Cambridge
United Kingdom
CB2 0Sw

Sponsor information

Organisation
University of Edinburgh

ROR
https://ror.org/01nrxwf90

Organisation
NHS Lothian

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Government

Funder Name
Chief Scientist Office, Scottish Government Health and Social Care Directorate

Alternative Name(s)
Chief Scientist Office, Scottish Government Health Directorate CSO, Chief Scientist Office, Scottish Government Health Directorates, Chief Scientist Office of the Scottish Government Health Directorates, Scottish Government Health and Social Care Directorate of the Chief Scientist Office, Scottish Government Health Directorate Chief Scientist Office, The Chief Scientist Office, CSO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
After publication, anonymised patient level study data may be shared with other researchers on reasonable request in writing to the Chief Investigator, Professor Rebecca Reynolds (R.Reynolds@ed.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Plain English results			29/04/2024	No	Yes

Study website	Study website	11/11/2025	11/11/2025	No	Yes