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Understanding the impact of metformin on maternal health and fetal growth in pregnancies complicated by maternal diabetes

Submission date
04/02/2021

Recruitment status
No longer recruiting

Registration date
15/02/2021

Overall study status
Ongoing

Last Edited
21/10/2025

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
Gestational diabetes mellitus (GDM) is high blood sugar (glucose) that develops during pregnancy and usually disappears after giving birth.
The prevalence of diabetes in pregnancy is increasing rapidly. Women with a combination of diabetes and vascular disease are six times more likely to develop fetal growth restriction. This means that whilst fetal overgrowth remains a common problem in women with hyperglycaemia, a very important minority of women (~3%) will develop placental disease leading to a small for gestational age infant.
Metformin is known to reduce fetal growth in pregnancies complicated by diabetes.
Current practice is to offer metformin to all women with diabetes (type 2 and gestational) irrespective of potential risk factors for placental disease. The effect of metformin on placental function and fetal growth is poorly understood. Given the uncertainty regarding the potential benefits, but possible negative effects on placental function and fetal growth highlighted by recent research, a trial of metformin in women hyperglycaemia and risk factors for placental disease is urgently needed.

Who can participate?
Women with type 2 diabetes and GDM, who have concomitant risk factors for the development of placental disease, for whom metformin would be routinely recommended

What does the study involve?
As part of routine care participants will be asked to monitor blood glucose levels at home. Participants will also be provided with diet and lifestyle advice to help improve glucose levels. If levels remain above the targets set for participants, we will discuss with participants the need for treatment with metformin tablets.
• Participants will be randomly allocated to treatment with diet & lifestyle (and insulin if required) or diet & lifestyle, metformin (and insulin if required)
• Participants will be asked to have an appointment and ultrasound scan (including 3D thigh volume measurements) every 4 weeks during pregnancy
• We will ask to record weight and take skinfold measurements and blood samples (2 teaspoons)

from participants at each hospital visit as part of the research
• We will ask to collect placenta and some blood samples from the baby's umbilical cord after birth
• We will record information regarding participants, pregnancy and the baby's birth details which will be stored on our protected research database
• We will ask to take some measurements from the baby after he/she is born which use a tape measure and skin callipers used to measure baby's skinfold thickness
• We will ask participants to visit the clinic with baby at 3-6 and 12 months of age for further measurements of weight and growth. At these visit we will ask to take blood samples from participants and measure height, weight and skinfold thickness.

What are the possible benefits and risks of participating?
Benefit: potential reduction in the need for insulin injections
The major potential disadvantage of taking part is that for women allocated to the 'no metformin' part of the study, insulin injections to control blood glucose levels may be required sooner than if metformin had been prescribed. However, we know that insulin is safe in pregnancy and is used in many hospitals as the first line treatment for diabetes in pregnancy.

Where is the study run from?
Manchester University Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
February 2021 to December 2025

Who is funding the study?
H2020 European Research Council

Who is the main contact?
Prof. Jenny Myers, jenny.myers@manchester.ac.uk

Contact information

Type(s)
Public

Contact name
Prof Jenny Myers

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-000599-13

Integrated Research Application System (IRAS)
288949

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 288949

Study information

Scientific Title
Metformin impact on maternal and infant cardiometabolic health

Acronym
MIMICH

Study objectives
In women with diabetes in pregnancy and risk factors for placental disease , what is the effect of withholding treatment with metformin versus usual care (including metformin) on fetal growth and maternal cardiometabolic health during pregnancy?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/07/2021, London - Chelsea Research Ethics Committee (Research Ethics Committee (REC) London Centre, 2 Redman Place, Stratford, London, E20 1JQ, UK; +44 (0)207 104 8029; Chelsea.rec@hra.nhs.uk), REC ref: 21/LO/0462

Study design
Open-label randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Diabetes in pregnancy

Interventions

Participants will be allocated 1:1 to the intervention (diet & lifestyle ± insulin) or standard care (diet & lifestyle, metformin ± insulin). Both groups will be offered insulin if fasting hyperglycaemia (≥5.3mmol/L) and/or postprandial hyperglycaemia (≥7.8mmol/L) persists. All other aspects of antenatal and delivery care will follow usual clinical care pathways underpinned by NICE 2015 guidelines for diabetes in pregnancy.

Duration of treatment – randomisation until end of pregnancy (maximum 34 weeks).

Randomisation – secure online platform with minimisation by gestation window, type of diabetes and risk factor for placental disease.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Insulin, metformin, insulin

Primary outcome(s)
Third trimester fetal growth velocity will be assessed by change in fetal growth zscore between 20-26 weeks (average) and birth.
(At each scan the estimated fetal weight (EFW) will be calculated using standard 2D biometry and fractional thigh volume (TVol) measurements using a standard formula and converted to a zscore (WHO). The delta change in zscore between the average zscore of scans performed between 20-26 weeks and the birthweight zscore will be calculated. In order to verify the primary outcome, the eCRF will capture the TVol measurement and the EFW at each scan as well as recording the 2nd trimester and 3rd trimester deviation scores. The source data (scan report) will verify the 2D biometry.)

Key secondary outcome(s))
1. Adherence/Acceptability
1.1. Number of missed doses– calculated as an average over pregnancy from the number of missed doses reported in the 7 days prior to each study visit (adjusted for number of study visits)
1.2. Undesirable effects of allocated treatment (number of women reporting undesirable effects associated with metformin and/or insulin/number of women receiving metformin or insulin treatment)
1.3. Treatment satisfaction with allocated medication regime (questionnaire)
1.4. Acceptability of allocated medication regime (questionnaire)
1.5. Secondary fetal growth outcomes:
1.6. Distribution of fetal growth zscores between treatment groups and within prespecified subgroups
1.7. Comparison of fetal growth zscores (conventional Hadlock formula EFW without TVol measurement) between treatment groups and within prespecified subgroups
1.8. Fetal growth velocity measured by growth potential realisation index (GPRI). (IGAP). https://igap.research.bcm.edu/ This online tool uses second trimester growth measurements to predict 3rd trimester growth for an individual fetus. The percentage deviation from the predicted growth is calculated and reported as GPRI.
1.9. Number of small and large for gestational age infants (defined using birthweight zscore)
2. Secondary maternal outcomes

2.1. Gestational weight gain (difference between baseline and 30-34 week visit weight adjusted for number of weeks)
2.2. Episodes of severe hypoglycaemia (blood glucose < 3mmol/L) – (total number reported over the treatment duration reported at each study visit)
2.3. Mean (fasting and 1 hour post meal) daily glucose and % time in target – captured from HBGM and/or CGM sensors at each study visit and summarised for each trimester
2.4. Maximum achieved dose of metformin (standard care arm only)
2.5. Total insulin dose (units/kg/day) at final study visit (short and long acting insulin reported separately)
2.6. Mean change in insulin dose (units/day) from baseline to last study visit
2.7. Need for antihypertensive therapy – study visits and pregnancy outcome case note review
2.8. Pre-eclampsia (defined according to ISSHP guidelines) - study visits and pregnancy outcome case note review
2.9. Indicated delivery (induction of labour or prelabour rupture of membranes (PROM) with stimulation of labour or pre-labour Caesarean section)- pregnancy outcome case note review
2.10. Mode of onset of birth (spontaneous, induction of labour, PROM with stimulation of labour, pre-labour Caesarean section) - pregnancy outcome case note review
2.11. Indication for onset of birth - pregnancy outcome case note review
2.12. Mode of birth - pregnancy outcome case note review
2.13. Post-partum haemorrhage (blood loss >1000mls) - pregnancy outcome case note review
2.14. Shoulder dystocia - pregnancy outcome case note review
2.15. Maternal skinfold measurements (delta change from baseline visit adjusted for gestation)
2.16. HOMA-IR (measured at 30-34 weeks) - measured in research blood samples (real time in the biochemistry lab)
3. Neonatal outcomes – clinical birth outcomes obtained from case note review
3.1. Fetal loss prior to 24 weeks' gestation
3.2. Fetal loss from 24+0 weeks' gestation (stillbirth)
3.3. Known early neonatal death (up to 7 days from birth)
3.4. Known late neonatal death (between 7 and up to 28 days from birth)
3.5. Gestational age at birth
3.6. Birthweight
3.7. Birthweight centile
3.8. Birthweight zscore
3.9. Neonatal unit admission (separation of baby from mother)
3.10. Principal recorded indication for neonatal unit admission
3.11. Length of stay in neonatal unit (and level of care) ,
3.12. Apgar score (5minutes)
3.13. Umbilical arterial pH at birth
3.14. Need for additional resuscitation at birth: intubation in the delivery room, resuscitation drugs or chest compressions
3.15. Need for respiratory support
3.16. Type of respiratory support needed
3.17. Need for treatment for neonatal hypoglycaemia
3.18. Type of treatment for hypoglycaemia
3.19. Lowest blood glucose measurement
3.20. Neonatal seizures
3.21. Intracranial haemorrhage
3.22. Necrotising enterocolitis
3.23. Time to reach full feeds without intravenous /parenteral nutrition support
4. Exploratory outcomes – additional research outcomes
4.1. Longitudinal changes in angiogenic markers (sFlt, PlGF) – measured in research blood samples (batch analysis end of study)

4.2. Maternal metabolic/inflammatory markers (hsCRP, IL-6, adiponectin) - measured in research blood samples (batch analysis end of study)
4.3. Total number of antenatal hospital inpatient days - pregnancy outcome case note review
4.4. Total number of postnatal hospital inpatient days - pregnancy outcome case note review
4.5. Ponderal index (fetal weight in grams X 100/(fetal length in centimeters) – measurement after birth
4.6. Neonatal measurements within 72 hours of birth (Crown-rump, crown-heel lengths, weight, arm, thigh, head, abdominal circumferences, biceps, triceps, subscapular skinfold thicknesses)
4.7. Cord blood C-peptide – measured in cord blood (batch analysis)
4.8. Erythropoietin (marker of intrauterine stress) - measured in cord blood (batch analysis)

Completion date
07/12/2025

Eligibility

Key inclusion criteria
1. Singleton pregnancy between 6+0 and 30+0 weeks' gestation inclusive
2. Aged 18 years or over and willing and able to give informed consent
3. Diagnosis of diabetes in pregnancy
3.1. Type 2 diabetes diagnosed before pregnancy and requiring pharmacological treatment
OR
3.2. Type 2/GDM diagnosed <24 weeks' gestation: abnormal glucose tolerance test, abnormal HBGM and/or HbA1C ≥42mmol/L
OR
3.3. GDM (diagnosed 24-30 weeks): HbA1C ≥39mmol/L and/or abnormal glucose tolerance test
4. Abnormal HBGMb (≤30 weeks)
5. Presence of at least one risk factor for placental disease
5.1. BP ≥130 and/or ≥80mmHg (clinic blood pressure)
5.2. Pulse wave velocity ≥ 9m/s
5.3. Age ≥35 years
5.4. Nulliparous
5.5. Pre-eclampsia and/or small for gestational age (<10th centile) in a prior pregnancy
5.6. Mean uterine artery PI ≥95th centile
5.7. Placental growth factor <10th centile
6. EFW ≤50th centile (if ≥22 weeks)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Total final enrolment
191

Key exclusion criteria
1. Medical contraindication to metformin
2. Known diagnosis of Type 1 diabetes
3. Multifetal pregnancy
4. Prior pregnancy complicated by shoulder dystocia

Date of first enrolment
20/10/2021

Date of final enrolment
30/04/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Manchester University Foundation Trust
Oxford Rd
Manchester
United Kingdom
M13 9WL

Sponsor information

Organisation
University of Manchester

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Government

Funder Name
H2020 European Research Council

Alternative Name(s)
H2020 Excellent Science - European Research Council, European Research Council, EXCELLENT SCIENCE - European Research Council, H2020 Ciencia Excelente - Consejo Europeo de Investigación (CEI), CIENCIA EXCELENTE - Consejo Europeo de Investigación, H2020 Wissenschaftsexzellenz - Für das Einzelziel 'Europäischer Forschungsrat (ERC)', WISSENSCHAFTSEXZELLENZ - Für das Einzelziel 'Europäischer Forschungsrat, H2020 Excellence Scientifique - Conseil européen de la recherche (CER), EXCELLENCE SCIENTIFIQUE - Conseil européen de la recherche, ECCELLENZA SCIENTIFICA - Consiglio europeo della ricerca, H2020 Eccellenza Scientifica - Consiglio europeo della ricerca (CER), ERC, CEI, CER

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request upon completion of the trial.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/10/2025	21/10/2025	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version v1		01/03/2021	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes