

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	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 15/02/2021	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 06/06/2025	Condition category Pregnancy and Childbirth	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> 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

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Additional identifiers

EudraCT/CTIS number

2021-000599-13

IRAS number

288949

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

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

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

See additional file ISRCTN13866189_PIS_v1_04February2021 (added 01/03/2021)

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 ($\geq 5.3\text{mmol/L}$) and/or postprandial hyperglycaemia ($\geq 7.8\text{mmol/L}$) 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 measure

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.)

Secondary outcome measures

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)

Overall study start date

01/02/2021

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 ≥ 42 mmol/L
 - OR
 - 3.3. GDM (diagnosed 24-30 weeks): HbA1C ≥ 39 mmol/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 ≥ 80 mmHg (clinic blood pressure)
 - 5.2. Pulse wave velocity ≥ 9 m/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 ≥ 95 th centile
 - 5.7. Placental growth factor <10th centile
- 6. EFW ≤ 50 th centile (if ≥ 22 weeks)

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Female

Target number of participants

225

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

England

United Kingdom

Study participating centre

Manchester University Foundation Trust

Oxford Rd

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Sponsor information

Organisation

University of Manchester

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Sponsor type

University/education

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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, H2020 Wissenschaftsexzellenz - Für das Einzelziel 'Europäischer Forschungsrat (ERC)', H2020 Ciencia Excelente - Consejo Europeo de Investigación (CEI), H2020 Excellence Scientifique - Conseil européen de la recherche (CER), H2020 Eccellenza Scientifica - Consiglio europeo della ricerca (CER), H2020 Doskonała Baza Naukowa - Europejska Rada ds. Badań Naukowych (ERBN), EXCELLENT SCIENCE - European Research Council, WISSENSCHAFTSEXZELLENZ - Für das Einzelziel 'Europäischer Forschungsrat, CIENCIA EXCELENTE - Consejo Europeo de Investigación, EXCELLENCE SCIENTIFIQUE - Conseil européen de la recherche, ECCELLENZA SCIENTIFICA - Consiglio europeo della ricerca, DOSKONAŁA BAZA NAUKOWA - Europejska Rada ds. Badań Naukowych, ERC, CEI, CER, ERBN

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

Results and Publications

Publication and dissemination plan

Peer review publication

Websites

Intention to publish date

01/06/2027

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?
Participant information sheet	version v1		01/03/2021	No	Yes
Protocol file	version 1.1	16/06/2021	07/09/2021	No	No
HRA research summary			28/06/2023	No	No