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# Preventing type 2 diabetes with metformin

**Submission date**
30/07/2018

**Recruitment status**
No longer recruiting

**Registration date**
02/08/2018

**Overall study status**
Completed

**Last Edited**
30/11/2023

**Condition category**
Pregnancy and Childbirth

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

## Plain English summary of protocol

Background and study aims
This study compares metformin versus placebo (dummy drug) for 1 year after delivery to prevent type 2 diabetes in women diagnosed with gestational diabetes in pregnancy. The aim of this study is to evaluate the study process, examine the acceptability of the intervention to mothers, and identify reasons for non-participation, non-adherence and withdrawal from the study. The study will also obtain preliminary estimates of the effects of metformin in preventing type 2 diabetes to inform a larger trial.

Who can participate?
Women aged 16 or over who have been diagnosed with gestational diabetes in pregnancy and are taking either insulin or metformin

What does the study involve?
Participants are randomly allocated to take either metformin or a placebo for a period of 1 year, during which time they are asked to attend three hospital visits to assess compliance, side effects and type 2 diabetes status. Some of the participants are also interviewed to assess the acceptability of the study.

What are the possible benefits and risks of participating?
The results of this study will aid the development of further trials examining the effectiveness of metformin at preventing type 2 diabetes in women with gestational diabetes. Patients may experience side effects from taking metformin. At the start of the treatment, the most common side effects are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. To prevent these, the dose will be adjusted for women who have not previously taken the medication to minimise any of these potential side effects. Very rare side effects (<1/10,000) from metformin include: lactic acidosis; decreased vitamin B12 absorption with decrease of blood levels during long-term use of metformin; isolated reports of liver function tests abnormalities or hepatitis resolving upon stopping metformin; and skin reactions such as erythema, pruritus and urticaria. Metformin is excreted into human breast milk but no side effects have been observed in breastfed newborns/infants. The research team will maintain contact with the participants throughout the study to monitor any side effects and advise accordingly. Participants will have an emergency number to contact, should they need to speak to a clinician out of hours.

Participants may have bruising, bleeding or discomfort from the blood samples. However, these are part of routine care and will be performed by a qualified member of the research team or a phlebotomist.

Where is the study run from?
1. The Royal London Hospital (UK)
2. Whipps Cross University Hospital (UK)
3. Newham University Hospital (UK)

When is the study starting and how long is it expected to run for?
March 2018 to July 2020

Who is funding the study?
1. Merck KGaA
2. Barts Charity

Who is the main contact?
Dr Zoe Drymoussi
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# Contact information

### Type(s)
Scientific

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# Additional identifiers

### Clinical Trials Information System (CTIS)
2017-004535-37

### Protocol serial number
37563

# Study information

### Scientific Title

Effectiveness and acceptability of metformin in preventing onset of type 2 diabetes after gestational diabetes in postnatal women: a feasibility study for a randomised, blinded, placebo-controlled trial

## Acronym
OMAhA

## Study objectives
A single site, double blind, randomised controlled feasibility study of metformin versus placebo for 1 year post-delivery to prevent type 2 diabetes in women diagnosed with gestational diabetes in pregnancy. The aim of the study is to evaluate the study process, examine the acceptability of the intervention to mothers, and identify reasons for non-participation, non-adherence and withdrawal from the study. The trialists will also obtain preliminary estimates of effects of metformin in preventing type 2 diabetes to inform a larger randomised controlled trial.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
London - Brent Research Ethics Committee, 16/05/2018, ref: 18/LO/0505

## Primary study design
Interventional

## Study design
Randomised; Interventional; Design type: Prevention, Drug

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Specialty: Reproductive Health and Childbirth, Primary sub-specialty: Maternal/ Fetal medicine; UKCRC code/ Disease: Reproductive health and childbirth/ Other maternal disorders predominantly related to pregnancy

## Interventions
Schedule for study participants
As many women as possible who are referred to obstetric diabetes antenatal care will be sent a Patient Information Sheet (PIS) with their hospital appointment letter inviting them to the clinic. Potential participants will be approached at the obstetric diabetic clinic by a member of the local research team to discuss participation in the study. Women will already have been diagnosed with Gestational Diabetes and will be taking either metformin or insulin. Women can also be consented at any subsequent antenatal visit prior to onset of labour. The woman's GP will be informed of her study participation.

For women who either decline to participate to consent or withdraw from the study, they will be invited to complete a short 5 minute questionnaire or a have a 5 minute interview to ask about their experience and any reasons for declining or withdrawal. The format of the questionnaire will depend on the situation and patient's preference.

It will be made clear that these are completely optional. In addition, the aim will be for a qualitative researcher to observe a proportion of the recruitment discussion. This is to gain a better understanding of how the way in which potential participants are approached and consented may affect trial participation and attrition. These will also be optional and the women will be free to decline the observation.

Women will be asked to provide the following at this visit:
1. Demographics: age, ethnicity, and education
2. Gestational age at diagnosis of GDM
3. Current treatment and dosage for GDM (e.g. metformin, or metformin and insulin)
4. What medication they are taking as well as the study medication
5. Singleton or multiple pregnancy
6. BMI at antenatal booking appointment
7. Pre-existing medical conditions (renal, hepatic, hypertension, and cardiac conditions)
8. Family history of diabetes
9. Oral glucose tolerance test findings in pregnancy
10. To complete a questionnaire of 6 questions about their current quality of life

After consent, 160 women are randomised to the intervention after delivery. 80 women are randomised to metformin, and 80 are randomised to a placebo. The placebo is identical in colour and size to the metformin. The use of a placebo in the trial is needed to recognise the psychological and biological effects of the treatment that is linked to the clinical setting. That way we can examine the true effect of the metformin.

Women will be given the study medication to take home with them. They will also be able to either download an app or be given the option of a paper diary to record how many tablets they have taken.

Women who had previously taken insulin rather than metformin during their pregnancy and are taking metformin for the first time will have their dose increased in increments for the first 3 weeks of the study. For 1 week they will take 1g metformin a day, followed by 1 week on 1.5g a day, and then 2g a day during the 3rd. They will receive weekly phone calls for the first 4 weeks from a member of the study team to check if there are any side effects and as a reminder to take the medication.

Women who were previously taking metformin during their pregnancy should not need any dose adjustments and will receive weekly text messages as a reminder to take the medication. Follow-up phone calls will be made if needed.

There will be 3 subsequent visits to the hospital that participants will be asked to attend.

Visit 1
Women will be seen by a member of the research team at a routine visit in the postnatal clinic, 6-13 weeks after being randomised to the study. At this visit, they will undergo the following tests:
1. 75g OGTT - a blood test is done to measure blood sugar, then the woman will be asked to drink a sugary liquid, wait for 2 hours and then this test is repeated. The test is to see how well the woman processes sugar. It is a routine test for women who have had gestational diabetes in pregnancy
2. HbA1c - this test is to diagnose type 2 diabetes
3. HOMA-IR - this is to test both the presence and extent of any insulin resistance that is currently expressed

4. c-peptide - this test is to find out how much insulin the body is producing
Women will be told the results of their OGTT and HbA1c as these are routine hospital tests. The HOMA-IR and c-peptide are tested as part of the study and participants will not be told the results of these.
They will also be asked the following:
1. How much they weigh
2. The weight of their baby
3. What medication they are taking as well as the study medication
4. Whether or not they are breastfeeding
5. Any side effects they have experienced from the medication
6. How much of the medication they have taken
7. To complete a questionnaire of 6 questions about their current quality of life

Between Visit 1 and Visit 2
Women will receive a phone call every 1 month, or every 2 months if adherence and tolerability is good, to document any side effects and promote adherence. Women will also receive text reminders once a month. In the final phone call prior to Visit 2, women will be reminded to discontinue metformin/placebo for one week prior to the visit. This wash-out period is to obtain accurate data of glycaemic control and identify any diabetes progression.

Visit 2
Women will be asked to attend a second visit 6 months after they have been randomised to the study. At this visit they will be asked for another blood sample for the following:
1. HbA1c
2. HOMA-IR
They will also be asked the following:
1. How much they weigh
2. The weight of their baby
3. What medication they are taking as well as the study medication
4. Whether or not they are breastfeeding
5. Any side effects they have experienced from the medication
6. How much of the medication they have taken

Between Visit 2 and Visit 3
Women will receive a phone call every 1 month, or every 2 months if adherence and tolerability is good, to document any side effects and promote adherence. Women will also receive text reminders once a month. In the final phone call prior to Visit 3, they will be reminded to discontinue metformin/placebo for one week prior to the visit. This wash-out period is to obtain accurate data of glycaemic control

Visit 3
Women will be asked to attend a third visit at 1 year after they have been randomised to the study.
At this visit they will be asked for a blood sample for the following tests:
1. HbA1c
2. HOMA-IR
3. OGTT
4. C-peptide
They will also be asked the following:
1. How much they weigh
2. The weight of their baby
3. What medication they are taking as well as the study medication

4. Whether or not they are breastfeeding
5. Any side effects they have experienced from the medication
6. How much of the medication they have taken
7. To complete a questionnaire of 6 questions about their current quality of life

Qualitative Research
10-15 women participating in the study will be invited to take part for the qualitative component of the trial. During the trial consent process, it will be explained to participants that the research team may want to interview them to hear more about their experiences with taking part in the study, and will ask the participant if they are willing to be contacted about an interview.

Interviews will be held approximately 2-3 months after the treatment has begun (around the same time as the 6-13 week follow-up appointment), and will explore participants' views on trial recruitment procedures in terms of who approached them about taking part, what the conversation was like, what kind of questions they had at the time and how these were answered. Interviews will explore participants' understanding of type 2 diabetes, reasons for participation in the trial and their perspectives on the study data collection methods. The interviews will also explore perceived acceptability and adherence with metformin in the postnatal period, the role of reminders and other intervention supports and factors influencing non-adherence. Interview schedules will be presented to a PPI (Patient and Public Involvement) advisory group called Katie's Team for development. A workshop will be conducted with participants from Katie's Team who reflect diversity in age, ethnicity, and parity.

There will be a second follow-up interview with approximately 5-8 of these participants towards the end of the treatment period (around the time of the 1-year assessment). The trialists will purposely include participants who found intervention adherence particularly difficult or easy in the early stages, to explore further the participant experience. Themes and concepts identified from the first set of interviews will also inform the issues raised in the second interviews. The trialists will also endeavour to interview a sample of women who drop out of the trial (number to be decided pragmatically as the trial progresses).

Interviews will be expected to last approximately 60 minutes and will be audio-recorded with participant consent. A separate consent form will be completed for women participating in the qualitative research interviews, before the interview commences. Participants will be offered a £10 voucher for each interview, as reimbursement for their time.

The trialists will conduct interviews with approximately 10 healthcare professionals, including those who are involved in delivering the intervention, and those involved in the care of women with gestational diabetes and women who develop diabetes in the postnatal period. The interviews with healthcare professionals will explore perspectives and experiences with the delivery of the intervention in practice, and perceived barriers and supports to the feasibility of its application in the postnatal period. Interviews with healthcare professionals will be expected to last approximately 60 minutes and will be audio-recorded. Written informed consent will be obtained by a trained and delegated member of the research team prior to any interview.

## Intervention Type
Drug

## Phase
Not Applicable

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

Metformin

### Primary outcome(s)
1. Proportion of eligible women of those screened, measured at baseline
2. Proportion of eligible women who give consent, measured at baseline
3. Proportion of randomised women, of those consented, measured at randomisation
4. Attrition rates, measured at 6-13 weeks, 6 months, and 12 months
5. Adherence rates with intervention, measured at 6-13 weeks, 6 months, and 12 months

### Key secondary outcome(s)
1. Acceptability outcomes: participants' views on the study and the intervention at 6-13 weeks and 12 months, and healthcare professionals' views on the barriers to recruitment, adherence and retention at the end of the study
2. Clinical and economic outcomes: maternal dysglycaemia, insulin metabolism laboratory tests at 12 months; breastfeeding and side effects at 6-13 weeks, 6 months, and 12 months; and EQ-5D-5L health and social care resource use and costs at 6-13 weeks, 6 months, and 12 months
3. Study conduct related outcomes: protocol deviations, issues with randomisation, monitoring findings, and any specific requests for support from healthcare professionals at the end of the study

### Completion date
01/07/2020

## Eligibility

### Key inclusion criteria
1. Women diagnosed with gestational diabetes as per the National Institute for Health and Care Excellence (NICE) criteria, at time of consent
2. Women who are on metformin and/or insulin in pregnancy
3. Aged 16 years or over at the time of consent

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Adult

### Sex
Female

### Total final enrolment
144

### Key exclusion criteria
1. Women unable to give informed, written consent in English
2. Pre-existing type 1 diabetes or type 2 diabetes
3. BMI > = 40 kg/m2

4. Known contraindications to metformin
5. Concurrent participation in another interventional clinical trial

### Date of first enrolment
15/08/2018

### Date of final enrolment
15/01/2019

## Locations

### Countries of recruitment
United Kingdom

England

### Study participating centre
**The Royal London Hospital**
United Kingdom
E1 1BB

### Study participating centre
**Whipps Cross University Hospital**
United Kingdom
E11 1NR

### Study participating centre
**Newham University Hospital**
United Kingdom
E13 8SL

## Sponsor information

### Organisation
Queen Mary University of London

### ROR
https://ror.org/026zzn846

# Funder(s)

**Funder type**
Industry

**Funder Name**
Merck KGaA

**Alternative Name(s)**
Merck, Merck Group, Merck KGaA, Darmstadt, Germany

**Funding Body Type**
Government organisation

**Funding Body Subtype**
For-profit companies (industry)

**Location**
Germany

**Funder Name**
Barts Charity

# Results and Publications

**Individual participant data (IPD) sharing plan**
The data sharing plans for the current study are unknown and will be made available at a later date.

**IPD sharing plan summary**
Data sharing statement to be made available at a later date

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | | 28/11/2023 | 30/11/2023 | Yes | No |
| Protocol article | protocol | 17/05/2020 | 15/01/2021 | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |