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Preventing gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource-poor settings

Submission date
21/01/2020

Recruitment status
Stopped

Registration date
25/02/2020

Overall study status
Stopped

Last Edited
04/04/2023

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
This is a feasibility study of a randomised clinical trial of metformin (compared with matched placebo) for the prevention of gestational diabetes and pregnancy hypertensive disorders (high blood pressure) in obese pregnant women. This study will help to determine whether it will be possible to recruit enough women to conduct a larger trial in the future, to measure if the routine administration of metformin could prevent gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource-poor settings (in Malawi and Zambia). Gestational diabetes (too much sugar in the blood in pregnancy) and pregnancy hypertensive disorders (high blood pressure that occurs in pregnancy) both cause maternal and neonatal deaths and long term problems. Gestational diabetes with an estimated global prevalence of 16% (with higher rates in South Asia and Africa) increases the incidence of adverse pregnancy outcomes. If left untreated it also increases the risk of future obesity and diabetes. Pregnancy hypertensive disorders account for 17.3% of maternal deaths in low-income countries, and are the second commonest cause of maternal death after haemorrhage (severe loss of blood).
In resource-rich countries, testing for gestational diabetes is routinely undertaken in women considered high risk, together with treatment of those affected and regular monitoring. Such an approach is difficult and inappropriate in resource-poor settings due to the high cost of testing of blood sugar monitoring and the lack of availability of suitable and cost-effective equipment. However, measurements of maternal body mass index (weight and height) cheaply and effectively identify obese women who are a high-risk group for both gestational diabetes and pregnancy hypertensive disorders. Additionally, one of the current treatments (metformin) for gestational diabetes is relatively cheap, widely available, and is safe, regardless of blood sugar levels. Recent evidence suggests that metformin might also reduce the incidence and severity of pregnancy hypertensive disorders. The aim of this study is to find out whether women are willing to be recruited and take medication. The researchers will then use this information to determine if a larger study to prevent gestational diabetes could be conducted in the future.

Who can participate?
Pregnant women (BMI > 26 kg/m2) attending antenatal clinics in Malawi

What does the study involve?
Women are randomly allocated to take either metformin or placebo oral tablets (500 mg slow release), up to 2000 mg daily from consent (first visit) until delivery.

What are the possible benefits and risks of participating?
The researchers cannot be certain whether there are any benefits of taking metformin. However, the results obtained might help improve future care for women who are overweight and pregnant in Malawi and at risk of developing diabetes. In the future, the researchers hope to conduct a larger study to confirm this and participation in PAPAGENO will help to develop further studies.

Where is the study run from?
The study is led jointly by teams in Edinburgh (UK) and Malawi

When is the study starting and how long is it expected to run for?
July 2019 to December 2020

Who is funding the study?
Funding has been provided by the UK Department for International Development (DFID), the National Institute for Health Research (NIHR), the UK Medical Research Council (MRC), and the Wellcome Trust under the Joint Global Health Trials Initiative (Project: MR/R019142/1)

Who is the main contact?
UK: Prof. Jane Norman
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Study website
https://www.ed.ac.uk/centre-reproductive-health/clinical-studies

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Version 1.0

Study information

Scientific Title
A Pragmatic Approach to Preventing GestAtional diabetes and preGnancy hypertENsive disOrders in obese pregnant women in resource-poor settings (PAPAGENO)

Acronym
PAPAGENO

Study objectives
The overall objective of this study is to determine the feasibility of a pragmatic placebo controlled-randomised trial of metformin to prevent gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource-poor settings.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/05/2019, LSHTM Pembroke Place, Liverpool, L3 5QA, UK Tel: +44 (0)151 705 3100), ref: 18/082
Approved 18/04/2019, NHSRC Ministry of Health and Populations (PO Box 30377 Lilongwe 3 Malawi; Tel: +265 (0)789 400), ref: 2180

Study design
Blinded randomised control trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format

Health condition(s) or problem(s) studied
Gestational diabetes mellitus

Interventions
Participants will be randomised to treatment (active or placebo) in a 1:1 ratio. Recruiting centre will be the only stratification variable, using simple randomisation under a randomly permuted block design. Randomisation will occur after eligibility has been confirmed and consent has been given. Women will then be randomised to one of the study treatments by selecting the next available medication pack.

Women will take the medication for a period between 12 and 30 weeks, depending on gestation at recruitment. Women will be prescribed metformin tablets in an incremental dose starting at 500 mg (1 tablet per day) increasing over 4 weeks up to 2000 mg (4 tablets per day). The first dose will be administered following consent (first visit between 12 and 28 weeks gestation). Women will be asked to start (week 1) with 500 mg metformin (1 tablet, once daily) taken with food in the evening, increasing in week 2 to total daily dose of 1000 mg per day (two tablets, one in the morning and one in the evening daily). In week 3 there will be a further increment to a total daily dose of 1500 mg per day (three tablets, one in the morning and two in the evening daily). In week 4 there will be a final increment to a total daily dose of 2000 mg (four tablets, two in the morning and two in the evening daily). Thereafter treatment is planned to continue at 2000 mg (four tablets) until women have delivered their baby. Women will be followed up for 28 days postnatally.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome measure
The ratio of women recruited, expressed as a fraction of the total number of women attending for antenatal care over the recruitment period, completed after the last patient last visit 28 days postnatally

Secondary outcome measures
1. Number of eligible women who are recruited into the study and provide written informed consent, completed after the last patient last visit 28 days postnatally
2. The proportion of pregnant women presenting at or before 28 weeks gestation (when the intervention will be started), calculated after the last patient last visit 28 days postnatally
3. Adherence to therapy, ascertained by review of diary and returned study medication, completed after the last patient last visit 28 days postnatally
4. Proportion of women in the placebo group and proportion of those in the active group (if tested prior to starting metformin) who have gestational diabetes at 24-30 weeks, completed after the last patient last visit 28 days postnatally
5. Ability to measure key clinical variables:
5.1. Proportion of women who are recruited but then lost to follow up for the primary and secondary outcomes, completed after the last patient last visit 28 days postnatally
5.2. Appropriate method to identify women and avoid double randomisation to address co-enrolment (i.e. GPS home identifiers, thumb or fingerprint), completed after the last patient last visit 28 days postnatally
5.3. Adverse events in each group monitored throughout the trial and presented to the Data Monitoring Committee, final presentation of the events completed after the last patient last visit 28 days postnatally

Overall study start date
01/07/2019

Completion date
31/12/2020

Reason abandoned (if study stopped)
This study was paused prior to recruitment of the first patient because of the impact of the COVID-19 pandemic. During the pause to the study, study drugs expired. Funding was insufficient to produce new study drugs or to continue the study, and in the face of the pandemic, it was considered that restarting this project was not a priority.

Eligibility

Key inclusion criteria
1. Pregnant women with a BMI ≥ 26 kg/m2
2. Pregnant women between ≥ 12+0 and ≤ 28+0 weeks gestation
3. Women estimated age ≥ 18 years
4. Women with a signed (and witnessed, if applicable) informed consent
5. Willing to be contacted, if necessary

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
100

Total final enrolment
0

Key exclusion criteria
1. Conditions identified in the current pregnancy, which exclude study participation:
1.1. Women with a BMI < 26 kg/m2
1.2. Pregnancy gestation > than 28+0 weeks
1.3. Women who are known to have a multiple pregnancy at the time of trial entry
1.4. Women who are currently lactating
1.5. Women known to have diabetes
1.6. Women who have been taking HIV antiretroviral medication for less than 6 months
1.7. Women currently taking dolutegravir
1.8. Acute conditions at the time of trial entry with the potential to alter renal function such as:
1.8.1. Dehydration sufficient to require intravenous infusion
1.8.2. Severe infection
1.8.3. Shock
1.8.4. Intravascular administration of iodinated contrast agents

1.9. Acute or chronic diseases which may cause tissue hypoxia such as:
1.9.1. Cardiac or respiratory failure
1.9.2. Pancreatitis
1.9.3. Recent myocardial infarction
1.9.4. hepatic insufficiency, acute alcohol intoxication, alcoholism

2. History of the following pre-existing conditions, at the time of trial entry:
2.1. Had a previous delivery of a baby <3rd centile for gestational age (e.g. a baby born ≥ 37 weeks gestation and the birthweight was ≤2.25 kg)
2.2. A known history in a previous pregnancy of gestational diabetes (needing drug treatment)
2.3. A known history of conditions affecting either the heart, lungs, liver, kidney or brain, which require regular medication at the time of recruitment
2.4. A known history of allergy to metformin or to any of the ingredients as listed in the current Summary Products Characteristics (SPC))
2.5. Known liver failure or dysfunction at the time of trial entry
2.6. Known severe renal failure or dysfunction at the time of trial entry
2.7. Known (any type of) acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
2.8. A previous known diabetic pre-coma
2.9. Previous known severe renal failure (GFR < 30 mL/min)

Note, the exclusion conditions listed in B above do not require additional testing to identify them. It is not currently clinical practice to perform formal testing for these conditions prior to giving metformin. Additionally testing to exclude all conditions will add an additional burden to Low Middle Income Country involved. However, the investigator(s) will review the woman's medical history by asking the woman questions and using available information to determine, if the woman has had any of these conditions.
Note, although metformin is not licensed for use during pregnancy its use in this scenario is endorsed by the National Institute for Health and Care Excellence.

Date of first enrolment
16/03/2020

Date of final enrolment
31/12/2020

Locations

Countries of recruitment
Malawi

Study participating centre
Area 25
Health Centre
Lilongwe
Malawi
-

Sponsor information

Organisation
University of Edinburgh

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Sponsor type
University/education

Website
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ROR
https://ror.org/01nrxwf90

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to Sponsors, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

The results will be communicated via open access primary publications, accessible review articles, conferences and invited presentations to clinicians, researchers, policy makers, funders and those working in pharma/industry. UK collaborators routinely post summaries of the research and links to publications on their website www.crh.ed.ac.uk. Local dissemination in UK, Zambia and Malawi is aided by seminar programs and interest groups

Communication to the general public will be facilitated by close links with charities such as Tommy's (www.tommys.org), who have a strong web presence and media engagement, and who also run a pregnancy information line.

Intention to publish date

01/04/2021

Individual participant data (IPD) sharing plan

The data will be held in Malawi by Malawi Epidemiology and Intervention Research Unit (MEIRU), access to the data will need to be sought via Dr Amelia Crampin and the Ministry of Health Malawi.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V1.1	18/03/2019	25/02/2020	No	Yes
Participant information sheet	version V1	18/03/2019	25/02/2020	No	Yes
Protocol file	version v1.0	07/03/2019	25/02/2020	No	No