

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

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<b>Registration date</b> 25/02/2020	<b>Overall study status</b> Stopped	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
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## 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/m<sup>2</sup>) 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?

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**Additional identifiers****Protocol serial number**

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

### **Study type(s)**

Prevention

### **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(s)**

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

**Key secondary outcome(s)**

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

**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  $\geq 26$  kg/m<sup>2</sup>
2. Pregnant women between  $\geq 12+0$  and  $\leq 28+0$  weeks gestation
3. Women estimated age  $\geq 18$  years
4. Women with a signed (and witnessed, if applicable) informed consent
5. Willing to be contacted, if necessary

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

Female

**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/m<sup>2</sup>
- 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

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## **Sponsor information**

**Organisation**

University of Edinburgh

**ROR**

<https://ror.org/01nrxf90>

## **Funder(s)**

**Funder type**

Research council

**Funder Name**

Medical Research Council

**Alternative Name(s)**

Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

### Funding Body Type

Government organisation

### Funding Body Subtype

National government

### Location

United Kingdom

## Results and Publications

### 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?
<a href="#">Participant information sheet</a>	version V1.1	18/03/2019	25/02/2020	No	Yes
<a href="#">Participant information sheet</a>	version V1	18/03/2019	25/02/2020	No	Yes
<a href="#">Protocol file</a>	version v1.0	07/03/2019	25/02/2020	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes