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Efficacy of metformin in pregnant obese women: a randomised controlled trial

Submission date
30/04/2010

Recruitment status
No longer recruiting

Registration date
14/06/2010

Overall study status
Completed

Last Edited
09/09/2016

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
The purpose of the study is to see if giving a tablet called metformin to pregnant women who have a raised body mass index (BMI) improves the mother's and baby's health. We know that having a raised BMI in pregnancy may cause the baby to grow too much in the womb. It may also cause other pregnancy complications. We also know that babies born to mothers who are overweight in pregnancy are slightly more likely to develop conditions such as diabetes or become overweight themselves in later life. We know that pregnant women with a higher BMI tend to have higher blood sugar. We believe this extra sugar may contribute to the complications associated with a higher BMI in pregnancy. We want to see if giving metformin to women who have a raised BMI in pregnancy improves the mothers and baby's health. Women with a raised BMI are 'insulin resistant', i.e. the body does not respond effectively to the insulin they make. This results in higher blood sugar levels. Metformin helps to improve insulin resistance and therefore prevent higher blood sugar levels. Therefore, it might improve pregnancy outcomes.

Who can participate?
Pregnant women aged between 16 and 40 who have a BMI of 30 kg/m2 or more can participate. They must be enrolled in the study before 16 weeks of pregnancy. They must have a singleton pregnancy (i.e. not twins or triplets) and be otherwise healthy.

What does the study involve?
If you chose to enroll in the study you will have an initial visit to the hospital before 16 weeks of pregnancy to complete a consent form and have some blood tests taken to ensure you are eligible to continue. This includes a test called a glucose tolerance test to make sure you do not have diabetes. Some body measurements will also be taken. You will be issued with a supply of tablets, which will be assigned to you by a process called randomisation. The tablets will either be the active treatment metformin, or an identical looking dummy tablet (placebo). Neither the study team nor you will know which group you are in. This is called 'double-blind'. You will be provided with instructions on how to take the tablets and a diary to record how many tablets you are taking. You will be asked to take the tablets every day until your baby is born. A member of the research team will complete a telephone questionnaire when you are 20 weeks pregnant to see how you are getting on. You will have two further visits to the hospital for repeat blood

tests and measurements at 28 and 36 weeks of pregnancy. When you have your baby some measurements will be taken of the baby's weight and size. There will be a final visit to the hospital to take body measurement of you and your baby when your baby is three months old. The pregnancy outcomes of women taking metformin will be compared with those taking the placebo.

What are the possible benefits and risks of participating?
We cannot promise there will any direct benefit to you from taking part but the information we obtain may help improve the future treatment of women who are pregnant with a raised BMI. The possible side effects of metformin treatment are nausea, vomiting, abdominal pain, diarrhoea and reduced appetite. Most people do not experience any side effects. Side effects are less likely if you start with a small dose and build it up gradually, which we will ask you to do.

Where is the study run from?
The study is run from the University of Edinburgh. There are 17 centres across the UK taking part including the Royal Infirmary, Edinburgh, Liverpool Women's Hospital and the University Hospital, Coventry.

When is the study starting and how long is it expected to run for?
February 2011 to April 2015

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Prof. Jane Norman
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Study website
http://www.crh.ed.ac.uk/empowar/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
EME 08/246/09

Study information

Scientific Title
A multicentre randomised placebo controlled clinical trial of metformin versus placebo in pregnant women to reduce the risk of obesity and metabolic syndrome in their babies

Acronym
EMPOWaR

Study objectives
Our study hypothesis is that metformin, administered to obese women during pregnancy, reduces the future life risk of obesity and metabolic syndrome in their babies. We will use high birthweight centile as a surrogate marker for future life events as its validity has been shown in large epidemiological studies.

Link to EME project website: http://www.eme.ac.uk/projectfiles/0824609info.pdf
Link to protocol: http://www.eme.ac.uk/projectfiles/0824609protocol.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland A Research Ethics Committee, 24/02/2010, ref: 10/MRE00/12

Study design
Multicentre randomised placebo-controlled clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Patient information can be found at: http://www.crh.ed.ac.uk/empowar/files/2011/12/EMPOWaR-PIL-current.pdf

Health condition(s) or problem(s) studied
Obesity, pregnancy

Interventions
Active arm:
Oral metformin tablets given three times daily to a maximum of 500 - 2500 mg daily. Total duration of treatment is from 12 weeks of gestation until delivery (maximum 30 weeks). Total duration of follow up in this study: one year after starting therapy.

Placebo arm:
Oral placebo tablets given three times daily. Total duration of treatment is from 12 weeks of gestation until delivery (maximum 30 weeks). Total duration of follow up in this study: one year after starting therapy.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome measure
Current primary outcome measures as of 05/11/2014:
Gestational age and sex adjusted birth weight centiles of the baby, measured at delivery of the baby

Previous primary outcome measures:
1. Gestational age and sex adjusted birthweight centiles of the baby, measured at delivery of the baby
2. Correlation between maternal insulin resistance (IR) at 36 weeks gestation
3. Adverse pregnancy outcomes, measured cumulatively as pregnancy progresses until after delivery

Secondary outcome measures
Current secondary outcome measures as of 05/11/2014:
1. Correlation between maternal insulin resistance (IR) at 36 weeks gestation and adverse pregnancy outcomes, measured cumulatively as pregnancy progresses until after delivery
2. More detailed measurements of neonatal body composition at birth including ponderal index, skinfold thickness and neonatal fat mass measured using air displacement plethysmography, measured within two weeks of birth
3. Biological mechanisms of metformin action including:
3.1. Change in whole body IR (longitudinal studies at 28 and 36 weeks) and hepatic and skeletal insulin sensitivity (36 weeks)
3.2. Maternal and neonatal inflammatory and lipid and fatty acid indices including C-reactive protein (CRP), interleukin-6 (IL-6), leptin, full lipid profile, non-esterified fatty acids,

polyunsaturated fatty acids and plasminogen activator inhibitor 1 (PAI1)/plasminogen activator inhibitor 2 (PAI2) ratio, measured at 36 weeks of pregnancy
3.3. Placental glucocorticoid receptor expression, measured in the placenta after delivery of the baby
3.4. Maternal brachial arterial endothelial dependent flow mediated dilatation (FMD), measured at 36 weeks of pregnancy
3.5. In vitro measurements of maternal myometrial contractility, measured after delivery
4. Changes in maternal anthropometry from the beginning to the end of pregnancy
5. Adverse pregnancy outcomes as a composite measured cumulatively until the end of pregnancy; incidence of low birthweight centile measured at delivery
6. Gas chromatography mass spectrometry measurements of metformin in maternal plasma to determine compliance in samples obtained at 36 weeks of gestation

Previous secondary outcome measures:
1. More detailed measurements of neonatal body composition at birth including ponderal index, skinfold thickness and neonatal fat mass measured using air displacement plethysmography, measured within two weeks of birth
2. Biological mechanisms of metformin action including:
2.1. Change in whole body IR (longitudinal studies at 28 and 36 weeks) and hepatic and skeletal insulin sensitivity (36 weeks)
2.2. Maternal and neonatal inflammatory and lipid and fatty acid indices including C-reactive protein (CRP), interleukin-6 (IL-6), leptin, full lipid profile, non-esterified fatty acids, polyunsaturated fatty acids and plasminogen activator inhibitor 1 (PAI1)/plasminogen activator inhibitor 2 (PAI2) ratio, measured at 36 weeks of pregnancy
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Overall study start date
01/02/2011

Completion date
30/04/2015

Eligibility

Key inclusion criteria
1. Caucasian obese (body mass index [BMI] greater than or equal to 30 kg/m^2) pregnant women between 12-0 and 16+0 weeks gestation
2. Women aged greater than 16 years
3. Signed informed consent form

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
400

Key exclusion criteria
1. Non Caucasian women
2. Women with a BMI less than or equal to 29 kg/m^2
3. Gestation greater than than 16 weeks
4. Women with pre-existing diabetes
5. Women with gestational diabetes in a previous pregnancy
6. Women with systemic disease requiring regular medication
7. Gestational diabetes in index pregnancy (diagnosed with 75 g oral glucose tolerance test [OGTT] prior to randomisation)
8. Previous delivery of a baby less than 3rd centile or previous pregnancy with pre-eclampsia prompting delivery before 32 weeks gestation
9. A known hypersensitivity to metformin hydrochloride or to any of the excipients
10. Known abnormalities of the liver (tested prior to randomisation)
11. Renal failure or renal dysfunction
12. Acute conditions with the potential to alter renal function such as:
12.1. Dehydration sufficient to require intravenous infusion
12.2. Severe infection
12.3. Shock
12.4. Intravascular administration of iodinated contrast agents
12.5. Acute or chronic diseases which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock or hepatic insufficiency, acute alcohol intoxication or alcoholism
13. Lactation
14. Multiple pregnancy

Date of first enrolment
01/02/2011

Date of final enrolment
30/04/2015

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre

University of Edinburgh
Edinburgh
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EH16 4TJ

Sponsor information

Organisation
University of Edinburgh and NHS Lothian (UK)

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Sponsor type
University/education

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Government

Funder Name
Medical Research Council (MRC)/National Institutes of Health Research (NIHR) (UK) - Efficacy and Mechanism Evaluation (EME) Programme (ref: EME 08/246/09)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	14/01/2015		Yes	No
Results article	results	01/10/2015		Yes	No
Results article	results	01/08/2016		Yes	No
HRA research summary			28/06/2023	No	No