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Randomised trial of pravastatin versus placebo for the prevention of high blood pressure in pregnancy

Submission date
11/11/2015

Recruitment status
Stopped

Registration date
18/11/2015

Overall study status
Stopped

Last Edited
26/03/2019

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims

Pre-eclampsia (PE) is a medical condition that ca affect pregnant women, usually from about 20 weeks or soon after their baby has been born. Early symptoms include high blood pressure and protein in the urine. In more severe cases, other symptoms may develop including severe headaches, vision problems, pain just below the ribs and swelling of the feet, ankles, face and hands (due to fluid retention). Most cases are mild, but, if left untreated, it can lead to severe complications for both mother and baby. These include eclampsia (life-threatening fits), stroke (due to high blood pressure) and HELLP syndrome (a liver and blood clotting disorder). There is a lot of evidence to suggest that the risk of severe complications occurring due to pre-eclampsia is much higher when the disease is severe and develops early (early onset) requiring the baby to be born before 37 weeks (preterm-PE). A major challenge in modern obstetrics is early identification of pregnancies at high risk of preterm- PE and undertaking of the necessary measures to improve placentation and reduce the prevalence of the disease. Extensive research, mainly as a consequence of the shift in screening for Down's syndrome from the second to the first trimester of pregnancy, has identified a series of early predictors of PE. A recent study involving more than 60,000 singleton pregnancies (that is pregnancies involving only one baby) examined at 11-13 weeks' gestation has demonstrated that a combination of maternal risk factors, including medical and previous obstetric history, the flow of blood through the uterine arteries (blood vessels which supply blood to the placenta), blood pressure and the measurement in the blood of proteins produced by the placenta (placental growth factor) can identify a high proportion of pregnancies at high-risk for PE. Consequently, there is a well described method for effective screening for preterm- PE at the time of routine screening for Down syndrome at 11-13 weeks’ gestation. Attempts at prevention of PE using various supplements and medications have failed or had limited success. There is therefore a continuing search for other therapeutic interventions for the prevention of PE. Pre-eclampsia shares similar risk factors with cardiovascular disease (for example, heart disease and stroke) and is thought to be either an early manifestation of cardiovascular disease unmasked by the pregnancy, or a risk factor for future cardiovascular disease. Statins are a group of medicines that can help lower blood cholesterol and are used to help prevent cardiovascular disease. Recent scientific research suggests that statins can reduce placental proteins that are involved in the development of PE.

The aim of the study is to examine if the use of pravastatin starting at 11-14 weeks' gestation in women at increased risk of developing pre-eclampsia helps to prevent the condition from developing or reduce its severity.

Who can participate?
Women (aged over 18) who are pregnant with one baby at 11-13 weeks gestation and identified as being of high risk for preterm-PE.

What does the study involve?
All women attending for the routine risk assessment for Down's syndrome at 11-13 weeks are screened for pre-eclampsia. Those that are then found to be at high risk of developing pre-eclampsia are offered the option of participating in the study. Those that agree are randomly allocated into one of two groups. Those in group 1 are given 20mg of pravastatin once a day until 36 weeks' gestation or after the birth of their baby (whichever comes first). Those in group 2 are given a placebo for the same time period. All participants are asked to visit their study centre at 19-24 weeks, 30-34 weeks and at 36 weeks. At these visits, a routine fetal scan, measurement of the flow of blood through the uterine arteries, blood pressure and the measurement of placental growth factor in the blood are carried out. They are also telephoned at 16 weeks and 28 weeks to address concerns and enquire about side effects and to make sure they are still taking the medication. They are also followed up by a further telephone interview 30 days after the last dose of medication.

What are the possible benefits and risks of participating?
Pre-eclampsia is a serious condition in pregnancy and at present there are no effective preventative treatment for women who are at high-risk. The main benefit of the trial is to obtain information that may be useful for the treatment of pre-eclampsia for women in future. Participants may benefit from the potential effect of pravastatin in preventing the onset and severity of the condition. Not all participants will gain benefit as half of them will receive a placebo drug. All participants will benefit from close monitoring that they will receive. Participants will not be denied anything they would usually receive as part of routine care by being part of this study. Statins have a good safety record in the general population and most patients do not experience side effects. If they do, these include headaches, nausea or vomiting, indigestion, constipation or diarrhoea, dizziness and muscular aches. Statins target the liver, therefore a liver function test will be checked before participants start treatment. Large studies have not demonstrated a link between statin exposure in pregnancy and congenital fetal malformations. Pravastatin is particularly safe as it does not easily cross the placenta (afterbirth) compared to other types of statins. Safety tests will be done at each of their follow-up visits and telephone consultations.

Where is the study run from?
Six NHS trusts in the UK.

When is the study starting and how long is it expected to run for?
March 2016 to March 2018

Who is funding the study?
Fetal Medicine Foundation (UK)

Who is the main contact?
Dr Liona Poon

Contact information

Type(s)
Scientific

Contact name
Dr Liona Poon

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Protocol serial number
FFIS/2015/01/ST

Study information

Scientific Title
RandomiSed conTrolled trial with prAvasTatin versus placebo for preventIoN of preeclampsia

Acronym
STATIN

Study objectives
Use of pravastatin starting at 11--14 weeks' gestation in women at increased risk of developing pre--eclampsia (high blood pressure in pregnancy) reduces the incidence and severity of this complication.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration.

Study design
Multicentre double-blind randomised controlled trial

Primary study design
Interventional

Study type(s)

Prevention

Health condition(s) or problem(s) studied
Pre-eclampsia

Interventions
All women attending for the routine risk assessment for Down's syndrome at 11-13 weeks will be screened for pre-eclampsia. Women will then be classified as high- and low risk for pre--eclampsia based on the combination of maternal history, biophysical findings (mean arterial blood pressure and uterine artery Dopplers) and biochemical factor (PlGF). Patients found to be at high risk of developing pre--eclampsia will receive information regarding the implications of this finding and will be offered the option of participating in a randomised study of pravastatin vs. placebo. Informed and written consent will be sought from those agreeing to participate in the study.

Study participants have an equal chance of being allocated into one of the two groups - pravastatin 20mg or placebo. The investigators, participants, and clinicians will not be aware of the treatment assignments. The participants will take one tablet daily from randomisation (11-14 weeks) until 36 weeks' gestation or earlier in the event of preterm delivery.

Follow--up clinical visits for all participants will be carried out at 19-24 weeks, 30-34 weeks and at 36 weeks. At these visits, a routine fetal scan, measurements of uterine artery Doppler, blood pressure, maternal blood levels of PlGF will be carried out. Trial participants will be telephoned at 16 weeks and 28 weeks to address concerns and enquire about side effects and compliance with medication. They will also be followed up by a further telephone interview 30 days after the last dose of medication.

Data on pregnancy and neonatal outcomes will be collected from the hospital maternity records or their general practitioners. In the event that the neonates are admitted to Special Care Baby Unit (SCBU)/Neonatal Intensive Care Unit (NICU), additional neonatal outcomes will be collected from the discharge summary of SCBU/NICU.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Incidence of preterm pre--eclampsia (PE) < 37 weeks

Key secondary outcome(s))
1. Incidence of early-PE (<34 weeks) and total PE (at any gestation)
2. Neonatal birthweight below the 3rd, 5th and 10th centile
3. Stillbirth or neonatal death due to any cause
4. Stillbirth or neonatal death ascribed to PE or fetal growth restriction
5. Stillbirth or neonatal death in association with maternal or neonatal bleeding
6. Rate of neonatal intensive care unit admission

7. Composite measure of neonatal mortality and morbidity
8. Placental abruption (clinically or on placental examination)
9. Spontaneous preterm delivery <34 weeks and <37 weeks

Completion date
06/03/2018

Eligibility

Key inclusion criteria
1. Age > 18 years
2. Singleton pregnancies
3. Live fetus at 11-13 weeks' of gestation
4. High-risk for preterm-PE at 11-13 weeks by the algorithm combining maternal history and characteristics, biophysical findings (mean arterial pressure and uterine artery Dopplers) and biochemical factors (placental growth factor)
5. English or Spanish speaking (otherwise interpreters will be used)
6. Informed and written consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Key exclusion criteria
1. Statin use in current pregnancy (administration must have ceased >28 days prior to randomisation)
2. Pregnancies complicated by major fetal abnormality identified at the 11-13 weeks assessment
3. Women who are unconscious or severely ill, those with learning difficulties, or serious mental illness
4. Women with contraindications for statin therapy
5. Hypersensitivity to Pravastatin or any component of the product
6. Active liver disease in the past 6 months (acute hepatitis, chronic active hepatitis) by medical history
7. Unexplained elevations (1.5x normal) of serum transaminases (ALT and AST), confirmed either by available blood results within the recruiting hospital in the last 6 months or blood taken prior to randomisation or jaundice
8. Women with any of the following conditions as it may predispose them to adverse events or side effects
9. Current (last 28 days) heavy alcohol use defined as ≥2 drinks per day

10. Illicit drug use
11. Amyotrophic lateral sclerosis (ALS)
12. Concomitant therapy with amiodarone, azole antifungals, diltiazem, gemfibrozil, nefazodone, nicotinic acid, protease inhibitors, efavirenz (non-nucleoside reverse transcriptase inhibitior), verapamil, fibrates, niacin (vitamin B3), cyclosporin, clarithromycin or erythromycin or other macrolide antibiotics
13. History of cholestasis of the liver in prior pregnancy
14. Personal or family history of myopathy or rhabdomyolysis
15. Women with any of the following medical conditions as described in medical record or patient history
16. Pregestational diabetes mellitus
17. Status post solid organ transplant
18. Chronic renal disease/insufficiency with baseline serum creatinine ≥1.5 mg/dL
19. Epilepsy or other seizure disorder
20. Uterine malformations
21. Cancer
22. Heart disease including prior myocardial infarction and prior cerebrovascular accident.
23. Concurrent and chronic (>6 months) use of medications with potential drug interactions with statins such as immunosuppressive drugs, gemfibrozil, niacin, erythromycin, itraconazole, cholestyramine, digoxin, rifampicin (Patients will not be excluded if the drug has been discontinued)
24. Inability to tolerate oral medications secondary to severe nausea and vomiting of pregnancy
25. Participating in another intervention study that influences maternal and fetal morbidity and mortality
26. Plans to deliver in a non-network site
27. Any other reason the clinical investigators think will prevent the potential participant from complying with the trial protocol

Date of first enrolment
07/03/2016

Date of final enrolment
04/09/2017

Locations

Countries of recruitment
United Kingdom

England

Spain

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Medway NHS Foundation Trust
Fifty Pembroke Court
Chatham Maritime Maritime Way
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N18 1QX

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E9 6SR

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SS0 0RY

Sponsor information

Organisation
Health Foundation for Education and Research in the Region of Murcia (Fundación para la Formación e Investigación Sanitaria)

ROR
https://ror.org/05m5has32

Funder(s)

Funder type
Charity

Funder Name
Fetal Medicine Foundation

Alternative Name(s)
FMF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

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?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes