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Randomised controlled trial with pravastatin versus placebo for prevention of preeclampsia

Submission date
26/02/2018

Recruitment status
No longer recruiting

Registration date
16/04/2018

Overall study status
Completed

Last Edited
10/05/2024

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Current plain English summary as of 01/07/2020:
Background and study aims
Preeclampsia is a serious pregnancy complication which can threaten the life and well-being of both the mother and the baby. There is a simple method of identifying women who are at very high risk of developing preeclampsia. During a hospital visit at 35 – 36 weeks of pregnancy, information is recorded about maternal characteristics (such as age, weight, and race) and medical history (such as chronic hypertension, diabetes, and if previous pregnancies were complicated by preeclampsia). A measurement is also taken of the woman's blood pressure and a blood sample is taken to measure levels of proteins that are associated with preeclampsia. A computer program then calculates the woman's chance of developing preeclampsia. Those women found to be at high risk are invited to participate in this study, which investigates whether the use of a drug called pravastatin can prevent the development of preeclampsia.

Who can participate?
Pregnant women age over 18 who are at high risk of preeclampsia

What does the study involve?
Participants are randomly allocated to take one capsule per day of either pravastatin or a matching placebo (dummy drug). Participants are asked to stop taking capsules at 41 weeks' gestation or in the event of early delivery, at the onset of labour (maximum duration of 42 days). The women have a follow-up visit 6 weeks after delivery. Incidence of preeclampsia with delivery is assessed by examination of patient hospital records and patient interviews.

What are the possible benefits and risks of participating?
The benefit for women taking part in the study is that they will know whether they are at high risk for developing preeclampsia or not. Those found to be at high risk will have more close monitoring of their blood pressure and the growth of their baby and they will benefit from such closer monitoring irrespective of whether they are allocated to the pravastatin or placebo group. If the study finds that pravastatin is useful in preventing preeclampsia, the women will benefit from such treatment in a future pregnancy, because women that get preeclampsia in one pregnancy are at much higher risk of developing preeclampsia in a future pregnancy. Extensive studies have reported that statins are not harmful to the fetus.

Where is the study run from?
1. King's College Hospital (UK)
2. The Royal London Hospital (UK)
3. Medway Maritime Hospital (UK)
4. North Middlesex Hospital (UK)
5. Homerton University Hospital (UK)
6. Southend University Hospital (UK)
7. Virgen de la Arrixaca (Spain)
8. Hospital Universitario La Paz (Spain)
9. Hospital de Torrejon (Spain)
10. CHU Brugmann (Belgium)

When is the study starting and how long is it expected to run for?
December 2016 to November 2020 (updated 08/10/2019, previously: March 2020)

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

Who is the main contact?
Prof. Kypros Nicolaides
eliza.tylki@nhs.net

Previous plain English summary :
Background and study aims
Preeclampsia is a serious pregnancy complication which can threaten the life and well-being of both the mother and the baby. There is a simple method of identifying women who are at very high risk of developing preeclampsia. During a hospital visit at 35 – 36 weeks at pregnancy information is recorded about maternal characteristics (such as, age, weight and race) and medical history (such as, chronic hypertension, diabetes, previous pregnancies complicated by preeclampsia). A measurement is also taken of the woman's blood pressure (MAP), an ultrasound machine measures the blood flow from the mother to the placenta (UTPI), and a blood sample is taken to measure the level of a protein produced by the placenta (PLGF). A computer program then calculates the woman's chance of developing preeclampsia. Those women found to be at high risk are invited to participate in this study, which investigates whether the use of a drug called pravastatin can prevent the development of preeclampsia.

Who can participate?
Pregnant women age over 18 who are at high risk of preeclampsia

What does the study involve?
Participants are randomly allocated to take one capsule per day of either pravastatin or a matching placebo (dummy drug). Participants are asked to stop taking capsules at 41 weeks' gestation or in the event of early delivery, at the onset of labour (maximum duration of 42 days). The women have a follow-up visit 6 weeks after delivery. Incidence of preeclampsia with delivery is assessed by examination of patient hospital records and patient interviews.

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3. Medway Maritime Hospital (UK)
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6. Southend University Hospital (UK)
7. Spitalul Filantropia Bucharest (Romania)
8. Virgen de la Arrixaca (Spain)
9. Hospital Universitario La Paz (Spain)
10. Hospital de Torrejon (Spain)
11. Ospedale Maggiore Policlinico (Italy)
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Prof. Kypros Nicolaides
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Contact information

Type(s)
Scientific

Contact name
Prof Kypros Nicolaides

Contact details
Fetal Medicine Research Institute
King’s College Hospital
London
United Kingdom
SE5 8BB
+44 (0)2032998256
eliza.tylki@nhs.net

Additional identifiers

EudraCT/CTIS number
2016-005206-19

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
33496

Study information

Scientific Title
Randomised controlled trial with pravastatin versus placebo for prevention of preeclampsia

Acronym
STATIN

Study objectives
Preeclampsia (PE) is an important cause of maternal and perinatal mortality and morbidity. A major challenge in modern obstetrics is early identification of pregnancies at high risk of PE and undertaking the necessary measures to reduce the incidence of the disease. Extensive research has demonstrated that the development of PE can be predicted by a combination of maternal demographic characteristics and medical and obstetric history and biophysical markers including uterine artery pulsatility index (PI) and mean arterial pressure (MAP) and biochemical markers including maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT-1). Although screening at 11-13, 20-24 and 30-34 weeks is effective at identifying pregnancies at high-risk of developing PE at < 37 weeks' gestation (preterm-PE) the performance of screening for term-PE is poor. Large multicentre studies have shown that although adverse outcomes for the mother and baby are more serious with preterm-PE the contribution of term-PE to such adverse outcomes is at least as high because the condition is much more common (incidence 0.5-0.7% for preterm-PE and 2-2.5% for term-PE). For example, in half of the maternal deaths from hypertensive disorders of pregnancy in the UK and Ireland at 2009-2014, the death occurred at > 37 weeks gestation. Effective screening for term-PE can be achieved by a combination of maternal factors, MAP, PLGF and sFLT-1 at the time of a routine ultrasound scan to monitor fetal growth at 35-37 weeks of gestation. The objective of this study is to examine if the prophylactic use of pravastatin from 35-37 weeks' gestation in women at increased risk for term-PE can reduce the incidence and severity of the disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - London Bridge Research Ethics Committee, 20/02/2017, ref: 17/LO/0130

Study design
Randomised; Both; Design type: Prevention, Drug, Cohort study

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, please use the contact details to request a patient information sheet: Anca Ciobanu: anca.ciobanu@nhs.net; Moritz Döbert: moritz.dobert@nhs.net

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

Interventions
Current interventions as of 01/07/2020:
This is a double-blind randomised placebo-controlled trial for which the eligible participants will be identified by a screening study. In the participating centres in Spain, Belgium and the UK, all women attending for their routine hospital visit in pregnancy at 35+0-36+6 weeks' gestation will be screened to identify a high-risk group for development of Preeclampsia (PE). In this visit the trialists will record maternal characteristics and medical history, measure the maternal MAP and serum PLGF and sFLT-1 and on the basis of these results estimate the risk for term-PE. Women that are screened positive for term-PE will be invited to participate in the randomised trial of pravastatin. Participants will take one capsule per day of either pravastatin 20mg or matching placebo. Participants will be asked to stop taking capsules at 41 weeks' gestation or in the event of early delivery, at the onset of labour (maximum duration of 42 days). The women will have a follow-up visit 6 weeks after delivery.

Previous interventions:
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Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome measure

Incidence of PE with delivery, assessed by examination of patient hospital records and patient interviews

Secondary outcome measures
Current secondary outcome measures as of 01/07/2020:
Assessed by examination of patient hospital records and patient interviews:
1. Adverse outcome of pregnancy at any gestation
2. Adverse outcome of pregnancy at ≥37 weeks' gestation
3. Stillbirth or neonatal death
4. Neonatal morbidity
5. Neonatal therapy
6. Incidence of low birth weight
7. sFLT-1 and PLGF value at 1 and 3 weeks after the onset of treatment
8. Pravastatin safety assessment during pregnancy: at 1 and 2 weeks after the onset of treatment, at term, 6 weeks after delivery

Previous secondary outcome measures:
Assessed by examination of patient hospital records and patient interviews:
1. Adverse outcome of pregnancy at any gestation
2. Adverse outcome of pregnancy at >37 weeks' gestation
3. Stillbirth or neonatal death
4. Neonatal morbidity
5. Neonatal therapy
6. Incidence of low birth weight
7. sFLT-1 and PLGF value at 1 and 3 weeks after the onset of treatment
8. Pravastatin safety assessment during pregnancy: at 1 and 2 weeks after the onset of treatment, at term, 6 weeks after delivery

Overall study start date
20/12/2016

Completion date
30/11/2020

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 01/07/2020:
1. Pregnant women without established preeclampsia
2. Singleton pregnancy
3. Live fetus at 35+0-36+6 weeks' gestation
4. Informed and written consent
5. Age ≥18 years
6. Not unconscious or very ill
7. No serious mental illness
8. No learning difficulties
9. Fluent in local language or translation by interpreter

Inclusion criteria for participant selection for RCT:
1. Same as for screening

2. Identified at screening as being at high-risk for term-PE by the algorithm combining maternal history and characteristics, MAP, PLGF and sFLT-1
3. Informed and written consent
4. No planned delivery within 7 days of planned randomisation date;
5. No major fetal abnormality;
6. No statin use within 28 days prior to randomisation;
7. None of the following contraindications for statin therapy:
7.1. Hypersensitivity to pravastatin or any component of the product
7.2. Lactose intolerance
7.3. Current or previous cancer
7.4. Previous solid organ transplant
7.5. Active liver disease (acute hepatitis, chronic active hepatitis) in the past 6 months
7.6. Chronic renal disease/insufficiency with baseline serum creatinine ≥1.5mg/dL
7.7. History of myopathy or rhabdomyolysis
7.8. ALT and/or AST levels ≥ 2 x the upper limit of normal
7.9. Creatine kinase levels ≥ 5 x the upper limit of normal
7.10. Concurrent and chronic (>6 months) use of medications with potential drug interactions with statins, such as immunosuppressive drugs, fibrates, gemfibrozil, therapeutic doses of niacin for hyperlipidaemia (low doses found in dietary/nutritional supplements such as pregnancy supplements may be used), protease inhibitors, efavirenz (non-nucleoside reverse transcriptase inhibitor), erythromycin, clarithromycin, itraconazole, cholestyramine, digoxin, rifampicin (patients will not be excluded if the drug has been discontinued, or is prescribed for a short duration of time)
7.11. Participating in another intervention study that influences the outcomes of this study

Previous participant inclusion criteria:
1. Pregnant women without established preeclampsia
2. Singleton pregnancy
3. Live fetus at 35+0-36+6 weeks' gestation
4. Informed and written consent
5. Age >18 years
6. Not unconscious or very ill
7. No serious mental illness
8. No learning difficulties
9. Fluent in local language or translation by interpreter
10. No major fetal abnormality
11. No statin use within 28 days prior to randomisation
12. None of the following contraindications for statin therapy:
12.1. Hypersensitivity to pravastatin or any component of the product
12.2. Lactose intolerance
12.3. Current or previous cancer
12.4. Previous solid organ transplant
12.5. Active liver disease (acute hepatitis, chronic active hepatitis) in the past 6 months
12.6. Chronic renal disease/insufficiency with baseline serum creatinine >1.5mg/dL
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itraconazole, cholestyramine, digoxin, rifampicin (patients will not be excluded if the drug has been discontinued, or is prescribed for a short duration of time)
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Inclusion criteria for participant selection for RCT:
1. Same as for screening
2. Identified at screening as being at high-risk for term-PE by the algorithm combining maternal history and characteristics, MAP, PLGF and sFLT-1
3. Informed and written consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 1120; UK Sample Size: 750

Total final enrolment
1129

Key exclusion criteria
Current participant exclusion criteria as of 01/07/2020:
For the randomised trial, same as for screening, but in addition:
1. Major fetal abnormality
2. Women with established PE
3. Statin use within 28 days prior to randomisation
4. Women with contraindications for statin therapy:
4.1. Hypersensitivity to pravastatin or any component of the product
4.2. Lactose intolerance
4.3. Current or previous cancer
4.4. Previous solid organ transplant
4.5. Active liver disease (acute hepatitis, chronic active hepatitis) in the past 6 months
4.6. Chronic renal disease/insufficiency with baseline serum creatinine ≥ 1.5mg/dL
4.7. History of myopathy or rhabdomyolysis
4.8. ALT and/or AST levels > = 2 x the upper limit of normal
4.9. Creatine kinase levels > = 5 x the upper limit of normal
4.10. Concurrent and chronic (>6 months) use of medications with potential drug interactions with statins, such as immunosuppressive drugs, fibrates, gemfibrozil, therapeutic doses of niacin for hyperlipidaemia (low doses found in dietary/nutritional supplements such as pregnancy supplements may be used), protease inhibitors, efavirenz (non-nucleoside reverse transcriptase inhibitor), erythromycin, clarithromycin, itraconazole, cholestyramine, digoxin, rifampicin

(patients will not be excluded if the drug has been discontinued, or is prescribed for a short duration of time)
5. Participating in another intervention study that influences the outcomes of this study

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For the randomised trial, same as for screening, but in addition:
1. Major fetal abnormality
2. Women with established PE
3. Statin use within 28 days prior to randomisation
4. Women with contraindications for statin therapy:
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5. Participating in another intervention study that influences the outcomes of this study

Date of first enrolment
16/08/2018

Date of final enrolment
30/11/2019

Locations

Countries of recruitment
Belgium

England

Spain

United Kingdom

Study participating centre
King's College Hospital
Windsor Walk 16-20
London
United Kingdom
SE5 8BB

Study participating centre
The Royal London Hospital
Whitechapel Rd
Whitechapel
London
United Kingdom
E1 1BB

Study participating centre
Medway Maritime Hospital
Windmill Road
Gillingham
United Kingdom
ME7 5NY

Study participating centre
North Middlesex Hospital
Sterling Way
London
United Kingdom
N18 1QX

Study participating centre
Homerton University Hospital
Homerton Row
London
United Kingdom
E9 6SR

Study participating centre
Southend University Hospital
Prittlewell Chase
Westcliff-on-Sea
United Kingdom
SS0 0RY

Study participating centre
Virgen de la Arrixaca
Ctra. Madrid-Cartagena, s/n, El Palmar

Murcia
Spain
30120

Study participating centre
Hospital Universitario La Paz
Paseo de la Castellana, 261
Madrid
Spain
28046

Study participating centre
Hospital de Torrejon
Calle Mateo Inurria, s/n, Torrejón de Ardoz
Madrid
Spain
28850

Study participating centre
CHU Brugmann
Place A.Van Gehuchten 4
Brussels
Belgium
1020

Sponsor information

Organisation
Fundación para la Formación e Investigación Sanitarias de la Región de Murcia

Sponsor details
Sponsor responsibilities for Trial Management are delegated to the Fetal Medicine Foundation (FMF) for sites in the UK and Belgium by the regulator, primary sponsor.
C / Luis Fontes PagÃ¡n No. 9
1st floor
Murcia
Spain
30003

Sponsor type
Hospital/treatment centre

Website
https://www.ffis.es/

ROR
https://ror.org/05m5has32

Organisation
King's College Hospital

Sponsor details
c/o Prof Kypros Nicolaides
Fetal Medicine Research Institute
London
England
United Kingdom
SE5 8BB
+44 (0)2032998256
eliza.tylki@nhs.net

Sponsor type
Hospital/treatment centre

Website
https://www.kch.nhs.uk/patientsvisitors/getting-to-kings

ROR
https://ror.org/044nptt90

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

Publication and dissemination plan
Planned publication in high-impact peer reviewed journals.

Intention to publish date
30/11/2021

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		01/06/2021	25/06/2021	Yes	No
HRA research summary			28/06/2023	No	No
Other publications		22/06/2023	10/05/2024	Yes	No