ISRCTN01879376 https://doi.org/10.1186/ISRCTN01879376

PHOENIX - Pre-eclampsia in HOspital: Early iNductIon or eXpectant management

Submission date
20/11/2013

Recruitment status
No longer recruiting

Registration date
25/11/2013

Overall study status
Completed

Last Edited
21/05/2024

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Main PHOENIX study
Background and study aims
Pre-eclampsia during pregnancy can be a very serious condition for both mother and baby. It can cause a sudden, rapid rise in blood pressure and cause seizures, strokes, multiple organ failure and on rare occasions, death. Babies whose mothers have pre-eclampsia tend to be smaller and more likely to be born prematurely or stillborn. The cause of pre-eclampsia is not known but it goes once a woman has given birth. The current guidelines state that women with pre-eclampsia should be hospitalized for careful monitoring and their labour induced once they reach 37 weeks of pregnancy. At 37 weeks of pregnancy, babies are generally considered to be fully developed (although most pregnancies go on to 40 weeks). Some doctors think, given that the complications of pre-eclampsia can be serious, that it would be better to induce labour before 37 weeks of pregnancy. The aim of this study is to find out whether inducing delivery earlier, when a woman is between 34 and 37 weeks of pregnancy, reduces the harm the condition can cause to the mother and baby despite the baby being born before they are considered to be fully developed.

Who can participate?
Women aged 18 or over who are between 34 and 37 weeks of pregnancy with confirmed pre-eclampsia but whose condition does not warrant immediate delivery.

What does the study involve?
Women are randomly allocated to either the Planned Delivery Group or the Expectant Management Group. At this point, women are given a questionnaire to complete which gathers information on their health before they give birth. Women allocated to the Planned Delivery Group are induced within 48 hours of being allocated to the group. Generally, women are given a hormone called prostaglandin as a vaginal gel/pessary to start their labour. If this does not work, other methods of inducing labour are tried following the hospital's standard procedures. Before delivery is induced, doctors may want to give a steroid injection to the mother to help her baby's lungs mature faster. Women allocated to the Expectant Management Group continue to be closely monitored in hospital until they reach 37 weeks of pregnancy. At this time (or shortly afterwards), their labour is induced in the same way as for women in the Planned Delivery Group. However, if their health or that of their baby worsens, they may be delivered before this time.

After delivery, women and their babies are cared for according to the hospital's standard practice regardless of the group they were allocated to. Information is collected on the health of the mother and baby until they are discharged from hospital. Six months after giving birth, women are sent a similar questionnaire to the one they completed whilst in hospital but the questionnaire also captures information on the NHS services that they have used since they were discharged. The questionnaire is again sent when their child reaches 2 years of age based on their due date. At this time a questionnaire is also sent to assess the health of their child.

What are the possible benefits and risks of participating?
It is difficult to separate the risks from the benefits of taking part in the study because they may balance each other out.
Women who are selected to be in the Planned Delivery Group may have their baby delivered up to 3 weeks (at 34 weeks of pregnancy) before they are usually fully developed (a baby is considered to be fully developed at 37 weeks but most pregnancies go on to 40 weeks). This may result in the baby having problems associated with being born early. However, letting the woman's pregnancy continue might harm them and their baby more. Women who are selected to be in the Expectant Management Group may become ill from the conditions associated with pre-eclampsia because their pregnancy is allowed to continue for longer. Also, their condition or that of their babys may suddenly worsen so that they have to be delivered quickly, which might be distressing. It is not yet known which of the two management strategies is the best and the aim of the study is to find this out.

Where is the study run from?
The study will be run initially from six hospitals with neonatal units to find out if the recruitment targets for the study can be met. It will then be opened up to approximately 34 more hospitals (40 in total).

When is the study starting and how long is it expected to run for?
April 2014 to January 2021

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

Who is the main contact?
1. Prof. Andrew Shennan (andrew.shennan@kcl.ac.uk)
2. Prof. Lucy Chappell (Lucy.chappell@kcl.ac.uk)

PEACOCK (PHOENIX-2) sub-study
Background and study aims
The cause of pre-eclampsia is not known, and it is not possible to tell which patients will get it more seriously. Researchers think there may be not such a good connection between the placenta and the mother’s womb. Some studies have shown changes in the blood level of a substance made by the placenta called Placental Growth factor (PlGF). This may be a useful test to help doctors decide which women and their babies are more at risk of becoming unwell. The aim of this sub-study is to improve how women between 34 and 37 weeks of pregnancy are assessed, by measuring the level of PlGF in their blood.

Who can participate?
Women aged 18 or over who are between 34 and 37 weeks of pregnancy with confirmed pre-eclampsia, but whose condition does not warrant immediate delivery.

What does the study involve?
Participants are asked for a small blood sample, about two teaspoons (12ml), which is tested for PlGF. Then, up until the time the baby is born they are asked for an extra blood sample at the same time as blood is taken for their regular tests. Apart from collecting the additional blood samples, the participants' treatment is not affected in any way. The results from these tests is not shared with participants or their doctors and so the care they receive is exactly the same as if they were not taking part. Information is collected about the participants and their babies' health until they are both discharged from hospital.

What are the possible benefits and risks of participating?
Measuring PlGF may help doctors improve the care for women with pre-eclampsia in the future. There are no expected serious side effects to having the blood test and blood tests are part of normal clinical care.

Where is the study run from?
The study will be run initially from six hospitals with neonatal units to find out if the recruitment targets for the study can be met. It will then be opened up to approximately 34 more hospitals (40 in total).

When is the study starting and how long is it expected to run for?
February 2016 to January 2021

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

Who is the main contact?
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PHOEBE (PHOENIX-3) study
Background and study aims
Pre-eclampsia can be a serious condition for both mother and baby. Most women with pre-eclampsia make a full recovery and their babies are healthy. However, pre-eclampsia can cause a sudden, rapid rise in blood pressure and in severe cases can cause fits, strokes, multiple organ failure and very rarely, death. It may restrict the flow of blood to the baby, so babies whose mothers have pre-eclampsia tend to be smaller and are more likely to be born early. Some studies have suggested that in some women, the woman's heart might have to work harder because of the pre-eclampsia. The aim of this sub-study is to find out how pre-eclampsia might have a long-term effect on a woman's heart. This will be done by looking at signs in the blood that may show that the heart has been working harder during pregnancy, and by taking a scan of the heart about six months after the baby is born.

Who can participate?
Women aged 18 or over who are between 34 and 37 weeks of pregnancy with confirmed pre-eclampsia, but whose condition does not warrant immediate delivery.

What does the study involve?
Participants are asked for a small blood sample, about two teaspoons (12ml). Then up until the time the baby is born participants are asked for an additional blood sample at the same time as their regular routine blood tests. After they have given birth, they are again asked for a small blood sample. Apart from collecting the additional blood samples, taking part in this sub-study does not affect treatment in any way. Information about participants and their babies' health is

collected until they are both discharged from hospital. At the end of the study, the blood samples are tested for substances that show how the heart is working. The results from these tests are not shared with participants or their doctors and so the care you receive is exactly the same as if they were not taking part in the sub-study. About six months after the birth of the baby, participants are asked to return to hospital to have an ultrasound scan which takes moving and still pictures of the heart, called an echocardiogram. It involves putting some gel on their chest, similar to any ultrasound scan they had when they were pregnant. From these pictures, the person doing the scan can see how the heart is working. This test takes about 20-30 minutes. The echocardiogram is being done for research purposes and so a clinical report is not produced. At the same visit, participants are also asked to give a small blood sample, about two teaspoons. Travel expenses for this part of the study are paid in the form of a voucher.

What are the possible benefits and risks of participating?
The person doing the echocardiogram looks to see if the heart is working normally. In a very few people, about 8 in 1000 women, a problem with their heart is found when they have this test. If this happens participants are offered a referral for an appointment with a heart specialist. This is expected to be needed for about three women in this sub-study. There are no expected serious side effects to having the blood samples taken and wherever possible blood samples for this sub-study are taken at the same time as having blood tests taken as part of routine maternity care.

Where is the study run from?
The study will be run initially from six hospitals with neonatal units to find out if the recruitment targets for the study can be met. It will then be opened up to approximately 34 more hospitals (40 in total).

When is the study starting and how long is it expected to run for?
February 2016 to January 2021

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

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
HTA 12/25/03; HTA 15/59/06; EME 15/23/02

Study information

Scientific Title
Pre-eclampsia in Hospital: Early Induction or Expectant Management

Acronym
PHOENIX

Study objectives
Study hypothesis: To determine whether planned delivery between 34+0 and 36+6 weeks of gestation in women with pre-clampsia reduces adverse maternal outcomes without substantially increasing neonatal/infant outcomes compared to the current recommended practice of expectant management and delivery at 37 weeks of gestation.

More details can be found at: https://www.journalslibrary.nihr.ac.uk/programmes/hta/122503/#/
Protocol can be found at: https://njl-admin.nihr.ac.uk/document/download/2007230

Added 05/10/2016:

PEACOCK (PHOENIX-2) sub-study: Prognostic indicators of severe disEAse in women with late preterm pre-eClampsia to guide deCision maKing on timing of delivery

Study hypothesis: To establish a prognostic model to inform optimal timing of delivery in women with late preterm pre-eclampsia, by comparing novel candidate biomarkers (e.g. plasma placental growth factor (PlGF)), with clinical and routinely collected blood/urinary markers to determine clinically indicated need for delivery within seven days of assessment.

Overall trial start date: 01/02/2016
Overall trial end date: 30/04/2018 - updated 18/07/2018: 29/02/2020
Target number of participants: 600 - updated 18/07/2018: 500
Recruitment start date: 01/04/2016
Recruitment end date: 30/04/2018 - updated 18/07/2018: 31/12/2018

More details can be found at: https://www.journalslibrary.nihr.ac.uk/programmes/hta/155906/#/

PHOEBE (PHOENIX-3) sub-study: Mechanisms of action of intervention in the PHOENIX trial: in women with preterm pre-eclampsia does planned delivery improve postpartum maternal cardiac function through attenuation of myocardial ischaemia at time of disease?

Study hypothesis: To examine the effects of delivery in women with late preterm preeclampsia, compared to expectant management and delivery at 37 weeks gestation on cardiovascular function at six months postpartum.

Overall trial start date: 01/02/2016
Overall trial end date: 30/04/2018 - updated 18/07/2018: 30/09/2019

Target number of participants: 404
Recruitment start date: 01/04/2016
Recruitment end date: 30/04/2018 - updated 18/07/2018: 30/11/2018

More details can be found at: https://www.journalslibrary.nihr.ac.uk/programmes/eme/152302/#/

Ethics approval required
Old ethics approval format

Ethics approval(s)
Hampshire B NRES Committee, 19/12/2013, ref: 13/SC/0645

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Pre-eclampsia in women between 34+0 and 36+6 weeks of gestation

Interventions
Planned immediate delivery of women with pre-eclampsia between 34+0 and 36+6 weeks of gestation versus expectant management and delivery at 37 weeks of gestation.

Women will be followed up to until their child is 2 years of age, corrected for prematurity. If a woman is enrolled at 34 weeks of gestation (the earliest time point at which they can be enrolled), the total duration of her participation in the study will be 28 months.

Added 05/10/2016:

PEACOCK (PHOENIX-2) sub-study:
Clinical, blood and urine parameters taken at the time of randomisation into the PHOENIX trial in women with late preterm pre-eclampsia.

PHOEBE (PHOENIX-3) sub-study:
Non-revealed blood test for biomarker assessment of myocardial ischaemia (e.g. for highly

sensitive cardiac troponin and Cardiac Myosin Binding Protein C), together with repeat non-revealed blood test and echocardiography with tissue Doppler studies at around 6 months postpartum.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Primary short-term maternal outcome:
Composite of maternal morbidity of fullPIERS (Pre-eclampsia Integrated Estimate of RiSk) outcomes with the addition of recorded systolic blood pressure >160 mmHg post randomisation.

Primary short-term perinatal outcome:
Composite of perinatal deaths (antenatal/intrapartum stillbirths and deaths within 7 days of delivery but not deaths due to congenital anomalies) or admissions to infant discharge.

Primary long-term infant outcome:
Neurodevelopmental assessment at 2 years of age (age corrected for prematurity) using PARCA-R Parent Report Composite.

Added 05/10/2016:

PEACOCK (PHOENIX-2) sub-study:
Primary short-term maternal outcome:
Clinically indicated need for delivery for pre-eclampsia (or related complications) within 7 days of assessment.

PHOEBE (PHOENIX-3) sub-study:
Primary long-term maternal outcome:
Composite of diastolic and systolic function classified according to the American College of Cardiology as assessed by echocardiography with tissue Doppler studies at 6 months postpartum.

Secondary outcome measures
Secondary short-term maternal outcomes:
Individual components of the composite primary outcome plus
1. Use of anti-hypertensive drugs
2. Progression to severe pre-eclampsia post-randomisation (defined as systolic blood pressure ≥ 160 mmHg, platelet count <100 x 109/litre, abnormal liver enzymes [ALT or AST >70 iu/litre])
3. Estimated fetal weight (on ultrasound scan) <10th centile post-enrolment
4. Absent or reversed end diastolic flow (on umbilical artery Doppler)
5. Time and mode of onset (spontaneous, induced or pre-labour caesarean section) and mode of delivery (spontaneous vaginal delivery, assisted vaginal delivery, caesarean section)
6. Confirmed thromboembolic disease requiring anticoagulation up to hospital discharge
7. Confirmed sepsis (positive blood or urine cultures) up to hospital discharge
8. Primary and additional indications for delivery in expectant management arm (maternal

hypertension not controlled by maximal therapy, biochemical abnormality, haematological abnormality, fetal compromise on ultrasound scan, fetal compromise on cardiotocography, severe maternal symptoms, 37 weeks gestation or specified other)

Secondary short-term perinatal outcomes:
1. Stillbirth post randomisation
2. Neonatal death prior to hospital discharge
3. Admission to Neonatal Unit (NNU)
4. Number of days in each category of care (intensive, high dependency, special, transitional and normal)
5. Total number of days in hospital
6. Birth weight (g)
7. Customised birth weight centile (GROW)
8. Birth weight <10th and <3rd customised centile
9. Gestational age at delivery
10. APGAR score at 5 minutes post birth
11. Umbilical arterial and venous pH (and base excess) at birth
12. Need for supplementary oxygen prior to discharge
13. Number of days when >2 hours of supplemental oxygen is required
14. Need for ventilation support (CPAP/high flow/endotracheal ventilation)
15. Abnormal cerebral ultrasound scan
16. Confirmed sepsis (positive blood or cerebrospinal fluid cultures)
17. Necrotising enterocolitis (Bells stage 2 and 3)
18. Seizures (confirmed by EEG and requiring anticonvulsant therapy)
19. Encephalopathy grade (worst at any time: mild, moderate, severe)
20. Hypoglycaemia (blood glucose <2.6 mmol/l on two or more occasions)
21. Other indications and main diagnoses resulting in NNU admission
22. Discharged home fully breast-fed

Secondary long-term maternal outcomes:
Maternal physical and mental health using the validated SF-12 questionnaire assessed at 6 months post delivery and 2 years (based on infant's age corrected for prematurity)

Health economic and quality of life outcomes:
1. Quality of life using the validated quality of life questionnaire EQ-5D immediately after randomisation, at 6 months and when the infant is 2 years of age corrected age for prematurity
2. Hospital attendances, nights and diagnostic tests from randomisation until delivery
3. Cost of delivery
4. Cost of neonatal care (hospital admissions, surgery and diagnostic tests)
5. Retrospective 6-month health/social care use by mother and infant at 6 months and 2 years
6. EQ-5D for the calculation of maternal quality-adjusted life-years (QALYs)

Added 05/10/2016:

PEACOCK (PHOENIX-2) sub-study:
1. Clinically indicated need for delivery for pre-eclampsia within 48 hours and within 14 days of assessment
2. Perinatal death
3. NNU admission

PHOEBE (PHOENIX-3) sub-study:
Diastolic blood pressure, systolic blood pressure, heart rate and cardiovascular components of the fullPIERS composite outcome (between enrolment and maternal discharge)

Overall study start date
01/04/2014

Completion date
26/01/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 05/10/2016:
1. Women between 34+0 and 36+6 weeks of gestation
2. Confirmed as having pre-eclampsia (as defined as defined by International Society for the Study of Hypertension in Pregnancy {ISSHP} 2014 statement)
3. Singleton or dichorionic diamniotic (DCDA) twin pregnancy
4. Aged 18 years or over at the time of screening
5. Able to give written informed consent

Previous inclusion criteria:
1. Women between 34+0 and 36+6 weeks of gestation
2. Confirmed as having pre-eclampsia (as defined by the NICE guidelines on Hypertension in Pregnancy)
3. An in-patient in a consultant-led maternity unit
4. Singleton or dichorionic diamniotic (DCDA) twin pregnancy
5. Aged 18 years or over at the time of screening
6. Able to give written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
900

Total final enrolment
901

Key exclusion criteria

Women will be excluded from participating in the study if a decision has already been made to delivery within the next 48 hours

Date of first enrolment
29/09/2014

Date of final enrolment
31/12/2018

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
St Thomas' Hospital
London
United Kingdom
SE1 7EH

Study participating centre
40 more participating hospital sites in the UK and Wales
United Kingdom
-

Sponsor information

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Sponsor type

University/education

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ROR
https://ror.org/0220mzb33

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Sponsor type
Hospital/treatment centre

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

United Kingdom

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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

Intention to publish date
01/02/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Lucy Chappell (lucy.chappell@kcl.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	28/01/2019	31/01/2019	Yes	No
Results article	results	28/09/2019	02/09/2019	Yes	No
Results article	Results of PEACOCK nested study of prognostic model	01/05/2021	25/05/2021	Yes	No
Results article	Cost-utility analysis	21/07/2022	22/07/2022	Yes	No
Funder report results		01/11/2022	13/12/2022	No	No
HRA research summary			28/06/2023	No	No

Results article	Secondary analysis of PHOEBE (PHOENIX-3) sub-study data	17/05/2024	21/05/2024	Yes	No