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Does repeat placental growth factor blood sample testing reduce harm from pre-eclampsia to babies?

Submission date
10/10/2019

Recruitment status
No longer recruiting

Registration date
25/11/2019

Overall study status
Completed

Last Edited
07/05/2024

Condition category
Pregnancy and Childbirth

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Pre-eclampsia is a condition occurring only in pregnancy, thought to be caused by the way the placenta implants into the wall of the womb. Women with pre-eclampsia can suffer from high blood pressure, problems with their kidneys, liver and blood clotting. The problems with the placenta can mean that the baby's growth is affected. In some cases the baby can be stillborn. Once diagnosed, the only cure is to deliver the baby. If pre-eclampsia occurs before 37 weeks of pregnancy, women may need to be admitted to hospital to have treatment and monitoring for complications, whilst planning for safe delivery of the baby. Some women become unwell very quickly and need to have their babies delivered; others have long stays in hospital. It can be difficult to identify women at high-risk of severe complications of pre-eclampsia. This study looks at the levels of a protein produced by the placenta called Placenta Growth Factor (PlGF). Women with suspected pre-eclampsia can have a simple blood test for this protein. Studies have shown that women with very low PlGF levels are at greater risk of severe pre-eclampsia and stillbirth. However, it is not known how PlGF levels change over time. When pre-eclampsia is suspected, it is difficult to predict how severely a woman and her baby will be affected. The aim of this study is to find out whether using repeated blood samples can help to reduce severe complications for babies, and for women.

Who can participate?
Pregnant women aged 18 or over suspected of having pre-eclampsia

What does the study involve?
If a woman agrees to take part, she will be asked to sign a consent form, and details about her and her pregnancy will be put into a secure computer database. This will also be noted in her hospital maternity records. The study computer will then select for her to have repeat PlGF-based blood tests with the results known or not known to her, her doctors and her midwives while she is pregnant. There will be a 50:50 chance of being in either study group. She will then have routine bloods to test for pre-eclampsia that will include her first PlGF-based test. Her doctor will then use the results of these tests to guide her care following their hospital standard practice. Depending on the result of the blood tests (including the PlGF-based test), the doctors

and midwives will decide if a woman needs to be admitted to hospital or how often they will need to see her again in her pregnancy to make sure she and the baby are okay. When she is asked to have repeat blood tests for routine follow up care, we will ask her for an extra 10 ml or two teaspoons of blood for a PlGF-based test. Depending on which study group she is in, the doctors and midwives will be given or not given the result of the PlGF-based test. If the doctors and midwives are given the PlGF-based test result, they can use this to guide ongoing care, in addition to following their hospital standard practice. If the doctors and midwives are not given the PlGF-based test results ongoing antenatal care will be exactly the same as if women were not taking part in the study. Women will only be asked to provide an extra blood sample for this study once per week or once every two weeks (depending on the result of the first test) and only for a maximum of four times during their pregnancy.

What are the possible benefits and risks of participating?
The first PARROT study showed that some women may spend less time in hospital, and if they have an abnormal result they may benefit from their doctors and midwives having more information about their pre-eclampsia condition. There are no expected serious side effects to having the blood tests and participants will be having blood tests as part of their normal clinical care.

Where is the study run from?
1. Guy's and St Thomas' NHS Foundation Trust (UK)
2. Manchester University NHS Foundation Trust (UK)
3. Leeds Teaching Hospitals NHS Trust (UK)
4. Liverpool Women's NHS Foundation Trust (UK)
5. Royal United Hospitals Bath NHS Foundation Trust (UK)
6. Bradford Teaching Hospitals NHS Foundation Trust (UK)
7. St George's University Hospitals NHS Foundation Trust (UK)
8. Kingston Hospital NHS Foundation Trust (UK)
9. Chelsea and Westminster Hospital NHS Foundation Trust (UK)
10. North Bristol NHS Trust (UK)
11. University Hospitals Bristol NHS Foundation Trust (UK)
12. Imperial College Healthcare NHS Trust (UK)
13. NHS Lothian (UK)
14. Ashford and St Peter's Hospitals NHS Foundation Trust (UK)
15. Croydon Health Services NHS Trust (UK)
16. Norfolk and Norwich University Hospitals NHS Foundation Trust (UK)
17. University College London Hospitals NHS Foundation Trust (UK)
18. Nottingham University Hospitals NHS Trust (UK)
19. Warrington and Halton Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
April 2019 to March 2023

Who is funding the study?
1. Moulton Charitable Trust (UK)
2. Tommy's Baby Charity (UK)

Who is the main contact?
Dr Louise Webster
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Contact information

Type(s)
Public

Contact name
Dr Louise Webster

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
265824; CPMS: 43092

Study information

Scientific Title
Placental growth fActor Repeat sampling for Reduction of adverse perinatal Outcomes in women with suspecTed pre-eclampsia

Acronym
PARROT-2

Study objectives
Repeat PlGF-based testing, in women presenting with suspected preterm pre-eclampsia, reduces adverse perinatal outcomes (perinatal death/neonatal unit admission).

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 11/11/2019, East of England - Cambridge East Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; Tel: +44 (0)207 104 8101; Email: NRESCommittee.EastofEngland-CambridgeEast@nhs.net), ref: 19/EE/0322

Study design
Multi-centre randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
Not available in web format

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

Interventions
Multi-centre RCT of revealed versus concealed repeat PlGF-based testing in women presenting with suspected pre-eclampsia between 22+0 and 35+6 weeks' gestation. The trial will be conducted in at least 15 maternity units across England. Recruitment will run for approximately 18 months in total.

All women participating in the trial will have an initial revealed PlGF-based test, allowing the clinician to formulate an individualised management plan.

Randomisation will be via a secure web-based platform (MedSciNet) with 50% of women assigned to revealed repeat PlGF-based testing and 50% of women assigned concealed repeat PlGF-based testing.

For the trial, the women will be asked to provide one extra tube of blood (as far as possible at the same time as clinical blood samples) up to four times during the rest of their pregnancy as per the schedule below. The results of the repeat PlGF-based test will be revealed to the health care professionals and the women in the intervention arm and used in addition to the other clinical features to inform ongoing management plan integrated with the NICE Hypertension in Pregnancy Guideline. The results of the repeat tests will be concealed in the usual care arm. It is recognised that some women will only provide one sample; from previous studies it is anticipated that most women will provide two samples as the majority of women will be delivered within that time interval.

For both the revealed repeat testing and concealed repeat testing groups, the repeat sampling strategy will be based on the first PlGF test result as follows:

1. If PlGF ≤100 pg/ml (including women <12 pg/ml) or sFlt-1/PlGF ratio >38, i.e. at higher risk, sampling will be weekly whilst attending for clinical review.
2. If PlGF >100 pg/ml or SFlt-1/PlGF ratio ≤38 (lower risk) and asymptomatic of pre-eclampsia, sampling will be every two weeks (+/- 7 days) whilst attending for routine antenatal checks. If a woman presents ≥7 days from last sample and is symptomatic, an additional sample can be taken and reported.

Women will only be asked to provide repeat samples while they are still pregnant and pregnancy outcome data for mother and baby will be collected by the site research teams from care records without the need for further review in person of the participants.

Intervention Type
Other

Primary outcome measure
Composite of:
1. Stillbirth defined as death of a fetus after 24 weeks' gestation and before birth collected by 6 weeks post birth
2. Early neonatal death defined as death occurring within the first 7 days of life collected by 6 weeks post birth
3. Neonatal unit admission defined as admission of the neonate to the neonatal unit and captured within the first 6 weeks from birth

Secondary outcome measures
Additional fetal and neonatal outcomes:
1. Late neonatal death defined as neonatal death occurring between 7 and 28 days after birth and captured from hospital records by 6 weeks post birth
2. Need for respiratory support on Neonatal Unit defined as the need for CPAP/high flow /endotracheal ventilation and recorded by 6 weeks post birth
3. Gestational age at delivery measured in days and recorded by 6 weeks post birth
4. Birthweight centile <10th calculated using recorded birth weight and using the Intergrowth 21 birthweight centile calculator and calculated by the trial statistician prior to data analysis

Added 07/07/2022:
5. Survival to discharge without severe morbidity: defined as survival to neonatal discharge without any of the following: bronchopulmonary dysplasia, retinopathy of prematurity, severe necrotising enterocolitis, brain injury, late-onset sepsis

Maternal secondary outcomes (between enrollment and delivery):
1. Proportion of women diagnosed with pre-eclampsia defined using the ISSHP definition and captured by 6 weeks post birth
2. Severe adverse maternal outcome composite defined by the fullPIERS consensus and captured by 6 weeks post birth
3. Systolic blood pressure ≥160 mmHg measured during routine blood pressure readings captured in maternity records and occurring on at least one occasion between study enrolment and birth of the baby
4. Concealed first repeat PlGF-based test performance (with comparison against currently utilised tests) for clinically indicated delivery for diagnosed pre-eclampsia within 14 days measured in peripheral blood samples at 1 to 3 weeks post study enrollment and analysed following completion of the trial

Health economic outcomes:
1. Perinatal: intensive care, high dependency and special care unit days measured as total of these days and captured by 6 weeks post birth
2. Maternal: antenatal outpatient attendances and inpatient days; intensive care unit use measured as total numbers of each of these antenatal care episodes and captured by 6 weeks post birth

Overall study start date
01/04/2019

Completion date
31/03/2023

Eligibility

Key inclusion criteria
1. Women aged 18 years or more between 22+0 and 35+6 weeks' gestation with clinical suspicion of pre-eclampsia
2. Viable singleton pregnancy
3. Able to give written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
1280

Total final enrolment
1252

Key exclusion criteria
Confirmed preterm pre-eclampsia at presentation

Date of first enrolment
06/12/2019

Date of final enrolment
30/09/2022

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
St. Thomas's Hospital
249 Westminster Bridge Road
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SE1 7EH

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House
Oxford Road
Manchester Greater
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M13 9WL

Study participating centre
Leeds Teaching Hospitals NHS Trust
Beckett Street
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LS9 7TF

Study participating centre
Liverpool Women's NHS Foundation Trust
Crown Street
Liverpool
United Kingdom
L8 7SS

Study participating centre
Royal United Hospitals Bath NHS Foundation Trust
Combe Park

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BA1 3NG

Study participating centre
Bradford Teaching Hospitals NHS Foundation Trust
Duckworth Lane
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Kingston Hospital NHS Foundation Trust
Galsworthy Road
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Chelsea and Westminster Hospital NHS Foundation Trust
369 Fulham Road
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United Kingdom
SW10 9NH

Study participating centre
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Southmead Road
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Marlborough Street
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W2 1NY

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EH1 3EG

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CR7 7YE

Study participating centre

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NR4 7UY

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
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NW1 2PG

Study participating centre
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
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Sponsor information

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Sponsor type
University/education

Website
https://www.kcl.ac.uk/

ROR
https://ror.org/0220mzb33

Organisation
Guy's and St Thomas' NHS Foundation Trust

Sponsor details
R&D Department 16th Floor
Tower Wing
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United Kingdom
SE1 9RT
+44 (0)207188 7188 Extension: 54426
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Sponsor type
Hospital/treatment centre

Website
https://www.guysandstthomas.nhs.uk/Home.aspx

Funder(s)

Funder type
Charity

Funder Name
Moulton Charitable Trust

Funder Name
Tommy's Baby Charity

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Primary responsibility for preparing publications will lie with the CIs, Professor Lucy Chappell and Dr Louise Webster. All publications using data from this trial to undertake original analyses will be submitted to the TSC for review before release.
The research will be published in high impact, peer reviewed, scientific journals. More general dissemination of the results will be achieved through publication of summary findings. There are no commercial or intellectual rights issues that would delay publication of results. The writing will be the responsibility of a writing committee drawn from the co-investigators (trial grant holders), trial co-ordinators and others substantially involved in execution, analysis and interpretation; and will be named authors on the principal publications arising from the trial provided they meet the authorship criteria used by most high impact peer reviewed journals see http://www.icmje.org.
Local PIs will be named formally as collaborators on the publication; PIs in non-recruiting centres and other trial personnel with significant input to the running of the trial will be named in the acknowledgements in publications. The CIs will nominate and agree appropriate authorship on all publications prior to commencement of writing.
Participants will be sent a summary of trial publications if they wish, with a reference to the final paper; and a copy of the journal article will be available on request from the CIs. This material will be offered to all the women recruited including those whose infants ultimately did not survive, although this group will first be asked if they wish to receive this information. As a policy, written dissemination will be in a style that is understandable and useable for all stakeholders including NHS commissioners, clinicians, funding bodies, service users, pre-eclampsia charities and the general public.
In order to target the clinical community, the results of this research will be disseminated by conventional academic outputs, including presentations at prominent national and international conferences.
Joint press releases will be coordinated by KCL and GSTT.
Links will be placed, or be encouraged to be placed, on other relevant web sites such as KCL, GSTT, NIHR and research user groups. Furthermore, we will ensure there is wider dissemination of the results via the participant support group Action on pre-Eclampsia (APEC) and appropriate social networks.

Intention to publish date
01/06/2023

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Louise Webster (louise.m.webster@kcl.ac.uk) and Lucy Chappell (lucy.chappell@kcl.ac.uk).
Type of data: quantitative
When the data will become available and for how long: 01/12/2022
By what access criteria data will be shared including with whom: to be determined at a later date
For what types of analyses, and by what mechanism: to be determined at a later date
Whether consent from participants was obtained: not applicable
Comments on data anonymisation: Data would only be supplied in fully anonymised format
Any ethical or legal restrictions: not aware of any
Any other comments: no

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		02/09/2022	05/09/2022	Yes	No
HRA research summary			28/06/2023	No	No
Results article		08/02/2024	12/02/2024	Yes	No
Results article		06/05/2024	07/05/2024	Yes	No