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The CRADLE-4 Trial: Can planned early birth in pre-eclampsia (high BP in pregnancy) reduce pregnancy complications in India and Zambia, compared to watchful waiting?

Submission date
27/11/2019

Recruitment status
No longer recruiting

Registration date
28/11/2019

Overall study status
Completed

Last Edited
03/07/2023

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 pregnancy complication. It is associated with high blood pressure and protein in the urine. It can be a serious condition for both mother and baby. For example, it can cause very high blood pressure and in severe cases it can cause fits, stroke and sometimes even death. Babies whose mothers have pre-eclampsia are smaller and are more likely to be born early. In severe cases pre-eclampsia may cause babies to be stillborn (intra-uterine fetal death). The cause of pre-eclampsia is not known. However, we know that the condition only improves once the baby is delivered.

Once a woman with pre-eclampsia has completed 37 weeks (8 ½ months) of pregnancy it is recommended that she is delivered. Her labour is normally started by induction (using medicines to start labour), between 37 and 38 weeks of pregnancy (around 8 ½ months). At this time most babies are fully developed and ready to be born. But, because pre-eclampsia can be serious and the mother and her baby might become unwell suddenly, it may be better for women with pre-eclampsia to deliver their babies earlier than this.

This study aims to find out whether, in women with pre-eclampsia between 34 and 37 weeks of pregnancy (around 7 ½ to 8 ½ months), planned early birth can reduce complications for the mother and her baby, compared to waiting until 37 weeks (about 8 ½ months) or until a serious problem occurs before this time.

This study may help improve the care of women with pre-eclampsia in the future.

Who can participate?

Women will be invited to take part in this study if they have pre-eclampsia and are between 34 and 37 weeks of pregnancy, but their condition does not require that their baby be delivered immediately.

What does the study involve?
If women decide they would like to take part we will ask them to sign a consent form.

Details about the woman and her pregnancy will be put into a computer which will randomly allocate her to either the planned early birth group or the watchful waiting group. Random allocation means that she cannot choose which group she wants to be in, and neither can her doctor. The computer will randomly allocate her - she will have a 50/50 chance of being in either group.

If she is allocated to the planned early birth group then her labour will be started by her doctor within two days. This is called an induction of labour (using medicines to start labour). The doctor might give her some steroid injections to help her baby's lungs mature. If she doesn't go into labour, her doctor may deliver her in other ways (including caesarean section), according to the hospital's protocol.

If she is allocated to the watchful waiting group then her doctors will look after her according to their routine protocol. This means she will be admitted to hospital and they will monitor her and her baby.

If she remains well until 37 weeks (about 8 ½ months) then her doctors will recommend delivery at this time. This means they will arrange for her labour to be induced (giving medicines to start labour) in the same way as for women in the planned early birth group. During monitoring, the doctors will recommend delivery before 37 weeks (about 8 ½ months) if they are concerned about either the mother's or the baby's condition. She will still be a part of the study if this happens.

After she has given birth, the woman and her baby will be cared for in the usual way at the hospital. Information will be collected about the woman and her baby's health until they are both discharged from hospital.

At the end of the trial, the outcomes of the mothers and babies in each group will be compared to establish whether the benefit of planned early delivery can reduce pregnancy complications and outweighs the risk of late preterm delivery to the baby. It is not currently known whether it is better to deliver at this time, or wait, which is why this research is being done.

What are the possible benefits and risks of participating?
There are possible risks and benefits for both groups. This is why we feel it is important to do this study to improve care for women with pre-eclampsia.

Women in both groups will undergo an induction of labour as this is the recommended management of pre-eclampsia. However, women in the planned delivery group will have their induction initiated earlier (within 48hrs after randomisation) whereas women in the expectant management group will undergo induction either when their clinical condition necessitates this due to progression of the disease, or, if they remain stable, when they reach 37 completed weeks of pregnancy. Previous studies have not shown any increased risk of caesarean section associated with induction and in fact the PHOENIX trial (another large study aiming to answer the same question but in a UK setting, http://www.isrctn.com/ISRCTN01879376) found that women who underwent planned delivery via induction between 34 and 37 weeks were more likely to have a vaginal delivery.

For women in the planned delivery group, whilst we know that the majority of babies born after 34 weeks do very well, there is a risk that their baby may need to go to the neonatal unit for a

short amount of time, and may need help with breathing and feeding in the first few days of life. The possible benefit of being in this group is that you avoid the risk of an emergency delivery and /or the complications of disease progression.

For women in the expectant management group, there is a risk that their condition may deteriorate and they may need an emergency delivery which could be distressing for both the mother and baby. In this scenario the baby may also need to go to the neonatal unit. The possible benefit of being in this group is that the baby may be more mature at the time of delivery.

Where is the study run from?
The study is organised by King's College London. It is taking place in India and Zambia.
1. Women and Newborn Hospital of University Teaching Hospitals, Zambia
2. Levy Mwanawasa University Teaching Hospital, Zambia
3. Ndola Teaching Hospital, Zambia
4. Jawaharlal Nehru Medical College KLE Dr. PBK Charitable Hospital, India
5. S.Nijalingappa Medical College & H.S.K.Hospital & Research Centre, India

When is the study starting and how long is it expected to run for?
October 2018 to May 2022

Who is funding the study?
1. Medical Research Council, UK
2. Department of Biotechnology , Ministry of Science and Technology, India

Who is the main contact?
1. Dr Alice Beardmore-Gray (public)
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2. Prof. Andrew Shennan
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
1.1

Study information

Scientific Title
The CRADLE-4 Trial: Planned early delivery versus expectant management to reduce adverse pregnancy outcomes in pre-eclampsia in a low and middle-income setting

Acronym
CRADLE-4

Study objectives
The aim of this trial is to establish whether planned early delivery in pre-eclampsia between 34+0 and 36+6 weeks can reduce adverse pregnancy outcomes compared to expectant management in a low and middle-income setting.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 24/10/2019, King's College London Research Ethics Committee (Franklin Wilkins Building, 5.9 Waterloo Bridge Wing, Waterloo Road, London, SE1 9NH; +44 (0)207 8484020; rec@kcl.ac.uk), ref: HR-19/20-135/35
2. Approved 13/09/2019, University of Zambia Biomedical Research Ethics Committee (Directorate of Research and Graduate Studies, University of Zambia, P. O. Box 32379, Lusaka, Zambia; +260 211 290258; drgs@unza.zm), ref: UNZA-301/3019
3. Approved 04/11/2019, National Health Research Authority Zambia (Paediatric Centre of Excellence, University Teaching Hospital, PO Box 30075, Lusaka, Zambia; +260 211 250309; znhrasec@gmail.com), ref: none provided
4. Approved 20/11/2019 S. Nijalingappa Medical College Institutional Ethics Committee (Navanagar, Bagalkot, 587102, Karnataka State, India; +91 835 4235340; iechsrsnmcbgk@gmail.com), ref: SNMCIEC/1.1/2019-2020
5. Approved 23/11/2019, KLE Academy of Higher Education and Research Institutional Ethics Committee (KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi, 10, Karnataka State, India; +91 831 2470400; kleclinicalresearch@gmail.com), ref: KAHER/IEC/2019-20/D-251119016

Study design
Multicentre unmasked individual randomised controlled trial

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 contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Timing of delivery in late preterm pre-eclampsia

Interventions
Randomisation will be managed by a secure web-based randomisation facility hosted by MedSciNet. The allocation ratio of intervention (planned early delivery) to control (expectant management) will be 1:1. Participants will be stratified by central site and minimised by parity (0 or ≥1), single/multi-fetal pregnancy (singleton or multi-fetal) and gestational age (34+0-34+6, 35+0-35+6, 36+0-36+6) at randomisation. MedSciNet will write the randomisation programme and hold the allocation code. Following randomisation, a clinician will then arrange for delivery or ongoing expectant management as the randomisation indicates.

In the intervention (planned early delivery) group planned delivery will be undertaken as soon as feasible (aimed to be commenced within 48 hours) after randomisation. Delivery will typically be

through induction according to local protocol (most commonly oral or vaginal administration of misoprostol). If induction fails, or is contraindicated, other management options including caesarean section should be considered. All options should be discussed with the pregnant woman and her needs and preferences taken into account. Use of steroids will be at the discretion of the clinician, in accordance with local guidelines.

The control group will receive routine expectant management which involves close monitoring of the maternal and fetal condition until the woman reaches 37 weeks, or a crisis develops necessitating delivery. This is in accordance with WHO guidelines which are followed at all of the proposed trial sites.

Intervention Type
Procedure/Surgery

Primary outcome measure
Primary maternal outcome:
Maternal mortality and morbidity based on the miniPIERS composite of adverse maternal outcomes, during pregnancy and delivery until primary hospital discharge with the addition of severe hypertension (systolic blood pressure of ≥160mmHg)

Primary short-term perinatal outcome:
Composite of stillbirths, neonatal deaths and neonatal unit admissions for >48hrs due to neonatal morbidity, until primary hospital discharge

Secondary outcome measures
During pregnancy and delivery until primary hospital discharge:
Secondary maternal outcomes:
1. Individual components of the primary outcome
2. Time and mode of onset (spontaneous, induced or pre-labour caesarean section) and mode of delivery (spontaneous vaginal delivery, assisted vaginal delivery, caesarean section)
3. Primary and additional indications for delivery in both arms
4. ICU admission
5. Length of stay
6. Time from randomisation to delivery
7. Use of Magnesium Sulphate
8. Use of Antenatal Corticosteroids
9. Use of Anti-hypertensives
Secondary perinatal outcomes will include:
1. Individual components of the primary outcome
2. Gestational age at delivery
3. Birthweight
4. Birthweight centile
5. Admissions to NNU (and main indication)
6. Total number of nights in hospital and number of nights in each level of care
7. Sepsis - with evidence of confirmed infection
8. Course of antibiotics given for Possible Serious Bacterial Infection (according to WHO's Integrated Management of Childhood Illness (IMCI) guidelines)
9. APGAR score at 5 and 10 minutes post-birth
10. Need for neonatal resuscitation
11. Hypoxic Ischaemic Encephalopathy and Grade
12. Neonatal seizures

13. Respiratory Distress Syndrome (RDS)
14. Supplementary oxygen & duration required
15. CPAP & duration required
16. Invasive ventilation support & duration required
17. Administration of surfactant
18. Hypo-glycaemia requiring intervention
19. Hypothermia (Temperature <36.5 degrees Celsius)
20. Neonatal jaundice requiring phototherapy
21. Necrotising enterocolitis (Diagnosed at surgery or resulting in death)
22. NG feeding required and indication
23. Exclusively breastfed at discharge from hospital

Overall study start date
03/10/2018

Completion date
12/05/2022

Eligibility

Key inclusion criteria
1. Able to give valid written, informed consent (in the countries where we are working the age of consent is 18 years old)
2. Viable ongoing pregnancy at time of recruitment
3. Clinical diagnosis of pre-eclampsia confirmed by the obstetric team: must fulfil minimum criteria of hypertension and proteinuria after 20 weeks' gestation. Hypertension will be defined as a systolic blood pressure of ≥ 140mmHg and/or a diastolic blood pressure of ≥90mmHg (or on anti-hypertensive drug at enrolment). Proteinuria will be defined as a 'positive' (≥ 1 + protein) urine dipstick result.
4. Gestational age between 34+0 and 36+6 confirmed by a doctor (as determined by known LMP date validated by early or late ultrasound scan if available)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
558

Total final enrolment
565

Key exclusion criteria
A decision to deliver within 48hrs has already been made by a senior clinician

Date of first enrolment
02/12/2019

Date of final enrolment
31/03/2022

Locations

Countries of recruitment
India

Zambia

Study participating centre
Women and Newborn Hospital of University Teaching Hospitals
Nationalist Road
Lusaka
Zambia
RW1X

Study participating centre
Levy Mwanawasa University Teaching Hospital
Great East Road, Chainama Area
Lusaka
Zambia
3170151

Study participating centre
Ndola Teaching Hospital
Broadway Road
Ndola
Zambia
10101

Study participating centre
Jawaharlal Nehru Medical College KLE Dr. PBK Charitable Hospital
Nehru Nagar
Belagavi
India
590010

Study participating centre
S.Nijalingappa Medical College & H.S.K.Hospital & Research Centre
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Sponsor type
University/education

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ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Department of Biotechnology , Ministry of Science and Technology

Alternative Name(s)
Dept. of Biotechnology, Govt of India, , , Department of Biotechnology, Department of Biotechnology, Ministry of Science & Technology, India, Department of Biotechnology, GOI, Dept. of Biotechnology, Govt. of India, Department of Biotechnology, Ministry of Sc & Tech, Govt of India, DBT

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
India

Results and Publications

Publication and dissemination plan
King's College London will coordinate dissemination of the results from this trial. 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.

Intention to publish date
01/02/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
Andrew Shennan (Andrew.Shennan@kcl.ac.uk)
Type of data: quantitative
When the data will become available and for how long: 01/12/2021
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:Consent will be gained for the research team to use participants data for future research if ethical approval from a research committee is

gained.
Comments on data anonymisation: Data would only be supplied in fully anonymised format.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	23/11/2020	25/11/2020	Yes	No
Results article		29/06/2023	03/07/2023	Yes	No