ISRCTN12033893 https://doi.org/10.1186/ISRCTN12033893

Calcium supplementation for prevention of pre-eclampsia

Submission date	Recruitment status	[X] Prospectively registered
19/05/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/05/2021	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
24/07/2025	Pregnancy and Childbirth	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Pre-eclampsia affects around one in 30 pregnancies in the UK. It usually presents with high blood pressure and protein in the urine but may also affect other organs in the body. While most women have a good outcome, the complications of pre-eclampsia can make women very unwell, and include fits and bleeding. The baby may also be affected by reduced growth and being born too early. In severe cases, the mother or baby may even die. The impact of the disease on women and their families is often considerable, related to the effect on their wellbeing as well as needing additional tests, admission to hospital and early delivery. This is also costly for the NHS.

At present doctors use aspirin to prevent pre-eclampsia in women who are more likely to develop it, but it only reduces the chance of getting pre-eclampsia by 10-20%. Delivery is the only cure.

Previous studies suggest calcium may be beneficial for preventing pre-eclampsia. However, most studies have been conducted in populations with low dietary calcium intake, so findings have not been viewed as applicable to a population with adequate calcium intake, such as in the UK. Moreover, little research has focused on the impact of calcium on women at high risk of pre-eclampsia.

This study will assess whether calcium supplementation during pregnancy along with usual antenatal care (including aspirin) is more effective than usual antenatal care alone in reducing the risk of pre-eclampsia in women who are at high risk.

Who can participate?

Pregnant women over the age of 16 years who are at high risk of developing pre-eclampsia based on various risk factors.

What does the study involve?

Once the women agree to participate in the trial, they will sign a consent form and be asked to provide information about their dietary calcium intake as well as general health (some information will also be taken from their medical notes). Half of the women will receive calcium tablets and the other half will receive placebo (dummy) tablets. The groups will be decided by chance, and neither the maternity team at the hospital, the research team, nor the participant will know which treatment they have received during the trial. The tablets will be started from

between 12 to 22 weeks' gestation, and taken until delivery, along with usual antenatal care (including aspirin). Participants will be asked to respond to text messages sent over their phone once a month to ask them how many of their tablets they have taken over the past week. Once the study is completed, information about pregnancy outcomes for the woman and her baby will be collected from medical notes.

What are the possible benefits and risks of taking part in the study?
By taking part in the study participants may reduce their risk of developing pre-eclampsia and its complications. It is also possible that participation may not lower their risk. The knowledge gained from their participation in this study will help inform future treatments and possibly lead to improved care for women at risk of pre-eclampsia.
Calcium supplementation given at the prescribed dose in this trial is unlikely to put the woman or her developing baby at risk of any side effects. However, as with taking any medication there is always a risk no matter how small. The rare side-effects reported for calcium are: feeling sick, stomach ache, constipation, diarrhoea, wind, or heartburn. Excessive calcium in the blood or urine can lead to very rare effects (less than 1 in 10,000 women) of skin rashes and itching and kidney stones or other kidney problems.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
November 2020 to July 2026

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

Who is the main contact?
Dr Shireen Meher
smeher@nhs.net

Contact information

Type(s)
Scientific

Contact name
Dr Shireen Meher

ORCID ID
https://orcid.org/0000-0002-9866-7932

Contact details
3rd Floor, Birmingham Women's Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TG
+44 (0)121 4721377
smeher@nhs.net

Type(s)
Public

Contact name
Mr Max Hughes

Contact details
Birmingham Clinical Trials Unit
School of Health and Population Sciences
Public Health Building
University of Birmingham
Birmingham
United Kingdom
B15 2TT
+44 (0)121 414 7023
cape@trials.bham.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2020-004435-25

Integrated Research Application System (IRAS)
262719

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 262719 RG 20-128, HTA - NIHR127325

Study information

Scientific Title
Calcium supplementation for Prevention of Pre-Eclampsia in high-risk women (CaPE)

Acronym
CaPE

Study objectives
In pregnant women at increased risk of pre-eclampsia, calcium supplementation given in a dose of 2 g/day during pregnancy plus usual care (including aspirin) is more effective than usual care alone at reducing the occurrence of pre-eclampsia.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 29/12/2021, East Midlands - Leicester Central Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)2071048181; leicestercentral.rec@hra.nhs.uk), ref: 21/EM/0281

Study design
Randomized triple-masked placebo-controlled multi-centre trial with a 12-month internal pilot and a health economic evaluation

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Prevention of pre-eclampsia in women at increased risk

Interventions
Pregnant women who meet the eligibility criteria of the trial will be randomised using a minimisation algorithm to ensure balance in treatment allocation (central randomisation, 1:1 ratio, with minimisation). Participants will be allocated to receive either calcium carbonate tablets 2 g/day (1g tablet twice daily) commenced from 12 to 22 weeks' gestation, taken until delivery, plus usual care (including aspirin), or to placebo tablets plus usual care.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Calcium carbonate

Primary outcome(s)
Pre-eclampsia, as defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP), assessed up to primary hospital discharge after birth

Key secondary outcome(s))
All secondary outcomes will be measured using patient medical records up to hospital discharge or 4 weeks after estimated delivery, whichever is sooner.

For the woman: Pre-eclampsia Core Outcome Set (COS) outcomes, namely:
1. Death
2. Eclampsia
3. Stroke
4. Visual impairment: retinal detachment or cortical blindness
5. Pulmonary oedema
6. Acute kidney injury: creatinine ≥90 µmol/l; 1 mg/dl
7. Liver capsule haematoma (confirmed on ultrasound)
8. Raised liver enzymes: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >40

IU/l
9. Low platelets < 150,000/µl
10. Abruption
11. Postpartum haemorrhage: estimated or measured blood loss ≥500 ml and ≥1000 after birth
12. Admission to Intensive Treatment Unit (ITU):
12.1. Any admission
12.2. Days of admission
13. Use of mechanical ventilation or intubation (for other than Caesarean section)

In addition to these core outcomes (woman), the researchers will record:
14. Gestational hypertension: new-onset hypertension ≥140/90 mmHg (at least two measurements several hours apart) after 20 weeks gestation in the absence of proteinuria or other features of pre-eclampsia
15. Severe hypertension: blood pressure ≥160 mmHg systolic and/or 110 mmHg diastolic
16. Severe pre-eclampsia, defined as pre-eclampsia with severe features (ACOG definition) including severe hypertension or low platelets <100,000 x 10e9/l, or abnormal liver function tests (LFTs) (liver enzymes at least twice the upper limit of normal) and right upper quadrant pain not accounted for by other diagnosis, or abnormal renal function (creatinine >1.1 mg/dl), or pulmonary edema or visual impairment or severe headache unresponsive to medication and no other cause found.
17. HELLP syndrome based on a clinician diagnosis, supported by low platelets and raised liver enzymes as defined above with or without evidence of haemolysis (raised LDH enzyme or blood film)
18. Preterm pre-eclampsia:
18.1. Diagnosed before 37 weeks
18.2. Diagnosed before 32 weeks
19. Use of magnesium sulphate for pre-eclampsia
20. Onset of birth: spontaneous, induction of labour or elective Caesarean section
21. Mode of birth: vaginal birth, assisted vaginal birth, Caesarean section (emergency or elective)
22. Adverse effects: maternal hypercalcaemia, renal stones, neonatal hypocalcaemia, stopping of medication due to adverse effects

For the baby: COS outcomes namely:
1. Any death in the baby up to hospital discharge. The researchers will collect data separately for:
1.1. Fetal loss <22 weeks gestation
1.2. Fetal loss ≥22 weeks' gestation (stillbirth)
1.3. Neonatal death (from birth up to 28 days)
1.3.1. Early neonatal death (up to 7 days after birth)
1.3.2. Late neonatal death (from 7 days up to 28 days)
1.4. Perinatal death – stillbirth or neonatal death up to 7 days
2. Gestational age at delivery (median, <28 weeks, <32 weeks, <37 weeks)
3. Birthweight (mean, <3rd centile, <10th centile)
4. Admission to NNU
4.1. Any admission
4.2. Days of admission
5. Neonatal brain injury - hypoxic-ischaemic encephalopathy requiring therapeutic hypothermia of neonatal stroke, severe intraventricular haemorrhage (IVH) grade III/IV and/or cystic periventricular leukomalacia

In addition to these core outcomes (baby), the researchers will record:
6. Level of neonatal care (admission to neonatal intensive care unit (NICU)/special care baby unit (SCBU))

7. Respiratory support morbidity
7.1. Surfactant use
7.2. Use of mechanical ventilation
7.3. Duration of respiratory support
8. Chronic lung disease (CLD) requiring oxygen therapy at 36 weeks post-menstrual age.
9. Necrotising enterocolitis (NEC) requiring surgery
10. Retinopathy of prematurity (ROP) requiring treatment with laser or anti-VEGF injection
11. Composite of death or serious morbidity: death or chronic liver disease (CLD), intraventricular hemorrhage (IVH) grade III/IV, necrotizing enterocolitis (NEC) requiring surgery or retinopathy of prematurity (ROP) requiring treatment

Completion date
31/07/2026

Eligibility

Key inclusion criteria
1. Over 16 years of age
2. Able to provide informed consent to participate
3. After a dating scan has confirmed viability (usually between 10 and 14 weeks gestation)
4. 22 weeks' 0 days gestation or less
5. Women deemed eligible for aspirin therapy based on NICE guideline criteria below where a woman has either:
5.1. One high-risk factor:
5.1.1. Hypertensive disease during a previous pregnancy
5.1.2. Chronic renal disease
5.1.3. Autoimmune disease such as SLE or antiphospholipid syndrome
5.1.4. Type 1 or 2 diabetes
5.1.5. Chronic hypertension
5.2. Or two or more moderate risk factors:
5.2.1. First pregnancy
5.2.2. Age more than 40 years
5.2.3. BMI ≥35 at first visit
5.2.4. Family history of pre-eclampsia
5.2.5. Multiple pregnancy
5.2.6. Pregnancy interval of 10 years or more
5.3. Or the Fetal Medicine Foundation (FMF) algorithm for pre-eclampsia risk assessment, as used locally
5.4. Or any other national pre-eclampsia screening criteria guidelines that may be used in the future

The study will also include women identified to be at high risk of pre-eclampsia based on any other national screening criteria guidelines that may be used in the future.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
16 years

Sex
Female

Key exclusion criteria
1. Any known contraindications to regular calcium intake (history of renal stones, known renal impairment with pre-pregnancy eGFR <30 ml/min/1.73m² or serum creatinine >150 (µmol/l), known history of hypercalcaemia or hypercalcaemia-causing diseases (e.g. parathyroid disease, sarcoidosis, malignancy), current severe persistent vomiting leading to dehydration or requiring hospitalisation (if persisting vomiting resolves, the patient may be re-assessed for inclusion in the trial, providing all other inclusion and exclusion criteria are met)
2. Use of drugs with potential for severe interactions with calcium: digoxin or other cardiac glycosides; antiretroviral drugs for HIV treatment, anti-neoplastic drugs, and diuretics (thiazide, thiazide-like or xipamide).
3. Use of any additional calcium supplement either on its own or as part of other multivitamin or Vitamin D preparations, and unwilling to stop them or change to other multivitamins, as this could lead to higher doses of calcium supplementation in the calcium group and contamination in the placebo group
4. Women who are taking vitamin D regularly in high doses >1000 IU/day, as supplements or for conditions such as malabsorption syndromes. Note: a short course of high dose Vitamin D (e.g., 20,000 IU weekly for 6 weeks) to treat Vitamin D deficiency during pregnancy is NOT an exclusion criteria
5. Known contraindications to excipient Isomalt (e.g. hereditary fructose intolerance)

Date of first enrolment
11/08/2022

Date of final enrolment
11/06/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Birmingham Women's Hospital
Birmingham Women's and Children's NHS Foundation Trust
Mindelsohn Way
Birmingham
United Kingdom
B15 2TG

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the CaPE trial management group (cape@trials.bham.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet			24/03/2023	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes

Protocol (other)			24/03/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes