

Preeclampsia prevention by timed birth at term

Submission date 01/11/2022	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 02/11/2022	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 14/04/2025	Condition category Pregnancy and Childbirth	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims?

Preeclampsia (PE) is a medical condition that can develop during pregnancy after 20 weeks of gestation. It is determined by high blood pressure and the presence of protein in the urine or the finding of maternal organ dysfunction. PE is one of the leading causes of maternal and perinatal death and disabilities. There is evidence to suggest some benefits to labour induction at or beyond term in women with PE, including a 67% reduction in perinatal death, an 8% reduction in the rate of caesarean section and a 12% decrease in neonatal intensive care unit admission. However, further evidence is required to establish whether early delivery in women could prevent PE in both the mother and their children. Therefore, the aim of this study is to establish whether screening for PE risk at 35-36 weeks' gestation and planning early-term birth for women at increased risk for PE, can reduce the incidence and severity of the disease as well as adverse pregnancy outcomes.

Who can participate?

Women aged over 18 years with a single pregnancy

What does the study involve?

Participants will be randomly allocated to either the intervention group or the control group. In the intervention group, planned early-term birth will be at 37, 38, 39, 40, or 41 weeks, depending on the women's PE risk, and following induction or by caesarean, as appropriate. Initiation of birth will be by labour induction (by local protocol) or elective caesarean (if indicated or desired by the woman) within the first 2 days of the gestational week, according to local protocol. In the control group birth will await the onset of spontaneous labour or the development of a clinical need for delivery.

What are the possible benefits and risks of participating?

Participants may benefit from a reduced chance of developing preeclampsia, which could have a positive impact on the health of both the mothers and the children. There is a risk of pain from the blood collection at two of the clinical visits. There are potential risks from elective caesarean and childbirth.

Where is the study run from?

King's College Hospital, London and Medway Maritime Hospital (UK)

When is the study starting and how long is expected to run for?
October 2022 to November 2024

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

Who is the main contact?
Prof. Kypros Nicolaides, Kypros@fetalmedicine.com

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number

315444

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

IRAS 315444, CPMS 54393

Study information

Scientific Title

Preeclampsia prevention by timed birth at term: a randomised trial

Acronym

INDUCTION

Study objectives

To determine the effect of screening and timing of delivery on the incidence of delivery with preeclampsia (PE).

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approval pending, London-Surrey Borders Research Ethics Committee (The Old Chapel, Royal Standard Place, NG1 6FS, UK; +44 (0)207 1048 088; surrey.rec@hra.nhs.uk)

Study design

Interventional randomized 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

Pre-eclampsia

Interventions

Randomisation will be provided by a computer-generated programme hosted by King's Clinical Trials Unit, in random permuted blocks, using a minimisation algorithm to ensure balance in the treatment allocation stratified for participating site.

Intervention group 1: Screening for PE at 35-36 weeks' gestation (by a combination of maternal factors, MAP, PlGF and sFlt-1) and planned early-term delivery if the risk for PE is increased, at a risk of at least 1 in 50.

Screening for PE will be undertaken by the 'competing-risks model' FMF algorithm that combines maternal demographics and medical history, MAP and maternal serum sFlt-1 and PlGF, to provide a personalised risk of PE. MAP will be measured by validated automated devices and a standardised protocol. Serum sFlt-1 and PlGF concentrations will be measured by an automated device (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany). Women will have a planned initiation of early-term delivery, according to their risk of PE, as follows:

In the intervention arm, planned early-term birth will be at 37, 38, 39, 40, or 41 weeks, depending on the women's PE risk, and following induction or by caesarean, as appropriate. Initiation of birth will be by labour induction (by local protocol) or elective caesarean (if indicated or desired by the woman) within the first 2 days of the gestational week, according to local protocol.

Control group 2: Usual care

Birth will await the onset of spontaneous labour or development of a clinical need for delivery, as per relevant NICE or RCOG clinical guidance on the timing of birth in general (ng207) or specific to maternal or fetal conditions (e.g., NG133 for pregnancy hypertension)

Trial timeline:

11-13 weeks – normal routine care and study information provided

20-22 weeks – normal routine care and study information provided

35-36+6 weeks – normal routine care and study information provided (randomisation if participants are eligible and consented to participant)

Intervention Type

Procedure/Surgery

Primary outcome measure

Delivery with PE as defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) 2021.14. The definition of PE is chronic hypertension or new onset

hypertension (systolic blood pressure (BP) should be ≥ 140 mm Hg and/or diastolic ≥ 90 mm Hg, on at least two occasions four hours apart BP $>140/90$ mm Hg) ≥ 20 weeks of gestation together with any of the following:

1. Proteinuria, defined as ≥ 300 mg in 24 hours or urinary creatinine ratio ≥ 30 mg/mmol (0.3 mg/mg) or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available; or
2. Maternal organ dysfunction, defined as any one of the following:
 - 2.1. Acute kidney injury with creatinine >90 $\mu\text{mol/L}$ or
 - 2.2. Liver involvement with elevated transaminases (alanine or aspartate aminotransferase [ALT or AST] >40 IU/L or twice the normal concentration) or
 - 2.3. Haematological complications (thrombocytopaenia with platelet count $<150 \times 10^9/\text{L}$), disseminated intravascular coagulation or haemolysis, or
 - 2.4. Neurological complications, such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata, or
3. Uteroplacental dysfunction, defined as estimated fetal weight (EFW) $<3\text{rd}$ percentile or EFW at the 3rd to 10th percentile in the presence of either of the following: uterine artery pulsatility index (UtA-PI) $>95\text{th}$ percentile, umbilical artery PI (UA-PI) $>95\text{th}$ percentile, or middle cerebral artery PI (MCA PI) $<5\text{th}$ percentile

All outcome measures will be recorded during the routine care appointment and during childbirth. When the participants do not give birth at the chosen hospital, then the outcome is taken from their medical record.

Secondary outcome measures

All outcome measures will be recorded during the routine care appointment and during childbirth. When the participants do not give birth at the chosen hospital, then the outcome is taken from their medical record.

1. Emergency caesarean section, defined as any caesarean section after spontaneous onset or induction of labour. A caesarean section without prior labour will be considered as elective
2. Neonatal care unit stay for ≥ 48 consecutive hours up to primary hospital discharge home or 28 days of life, whichever is earlier

Other secondary outcomes:

1. GH, defined as systolic BP ≥ 140 mm Hg and/or diastolic ≥ 90 mm Hg, on at least two occasions 4 hours apart, and developing at ≥ 20 weeks' gestation in previously normotensive women (i.e., BP $<140/90$ mm Hg)
2. Components of the 2021 ISSHP definition of PE (as above)
 - 2.1. PE as defined by ACOG 201915:
 - 2.2. GH (as above) or severe hypertension (as below), and either
 - 2.3. Proteinuria (as above) or
 - 2.4. In absence of proteinuria, one/more of:
 - 2.4.1. Pulmonary edema
 - 2.4.2. Platelet count $<100 \times 10^9/\text{litre}$
 - 2.4.3. Serum creatinine >97 $\mu\text{mol/L}$ or a doubling in its value
 - 2.4.4. Abnormal liver enzymes (ALT or AST >67 IU/litre)
3. 'Severe features' of PE (one or more), and its components, according to ACOG 201915 and without alternative diagnoses:
 - 3.1. Severe hypertension (as defined below)
 - 3.2. Platelet count $<100 \times 10^9/\text{L}$
 - 3.3. ALT or AST raised to twice normal (>67 IU/L) and persistent severe right upper quadrant abdominal or epigastric pain unresponsive to medication and not otherwise accounted for by

alternative diagnoses

3.4. Serum creatinine $>97 \mu\text{mol/L}$ or a doubling of value in the absence of other renal disease

3.5. Pulmonary edema

3.6. New-onset headache unresponsive to medication

3.7. Visual disturbances

4. Preeclampsia Integrated Estimate of Risk Score (PIERS) combined adverse maternal outcome, and its components, derived from Delphi consensus (with the exception of the Glasgow coma score <13):

4.1. Maternal death

4.2. Central nervous system complications (one or more of):

4.2.1. Stroke (acute neurological event with deficits lasting $> 24 \text{ hr}$, not due to a post-ictal state)

4.2.2. Eclampsia (generalized convulsion in the absence of a history of epilepsy)

4.2.3. Blindness (either retinal or cortical, defined as loss of visual acuity in the presence of intact pupillary response to light)

4.3. Cardiorespiratory complications (one or more of):

4.3.1. Uncontrolled hypertension (requiring administration of 3 or more different parenteral [intravenous or intramuscular] antihypertensive agents within a 12-hour period)

4.3.2. Inotropic support (use of vasopressors to keep systolic BP $>90 \text{ mmHg}$ or a MAP $>70 \text{ mmHg}$)

4.3.3. Pulmonary oedema (diagnosed clinically with one/more of oxygen saturation $< 95\%$, diuretic treatment or x-ray confirmation)

4.3.4. Respiratory failure (intubation, ventilation by endotracheal tube or non-invasively, or need for $> 50\%$ oxygen for $> 1 \text{ hr}$ which is not due to caesarean delivery)

4.3.5. Myocardial ischemia or myocardial infarction (by characteristic ECG changes and markers of myocardial necrosis)

4.3.6. $\text{SpO}_2 <90\%$

4.4. Haematological complications (one or more of):

4.4.1. Platelet count $<50 \times 10^9/\text{L}$

4.4.2. Transfusion (of any blood product)

4.5. Hepatic complications (one or more of):

4.5.1. Dysfunction (INR >1.2 in the absence of DIC or treatment with warfarin, OR, in the presence of DIC or treatment with warfarin: either mixed hyperbilirubinemia $>17 \mu\text{M}$ or hypoglycemia $<2.5 \text{ mM}$) in the absence of insulin)

4.5.2. Hepatic haematoma or rupture (presence of a blood collection under the hepatic capsule as confirmed by imaging or at laparotomy)

4.6. Acute kidney injury:

4.6.1. Acute serum creatinine $>200 \mu\text{M}$ with pre-existing renal disease

4.6.2. Acute serum creatinine $>150 \mu\text{M}$ with no pre-existing renal disease

4.6.3. Dialysis

4.7. Placental abruption (clinically or on placental examination)

4.8. Other (as detailed, with appropriate information from hospital records)

5. Core maternal outcome set for PE17 (one or more of) and its components:

5.1. Maternal mortality

5.2. Central nervous system complications: eclampsia, stroke, blindness that is retinal or cortical (as defined for PIERS)

5.3. Cardiorespiratory complications: pulmonary edema, respiratory failure (as defined for PIERS)

5.4. Platelet count $<100 \times 10^9/\text{L}$

5.5. Hepatic complications: AST or ALT raised to twice normal, or haematoma (as for PIERS)

5.6. Acute kidney injury (as for PIERS)

5.7. Placental abruption

5.8. Postpartum haemorrhage (defined as blood loss $\geq 1 \text{ L}$ within the first 24 hours after birth)

5.9. Maternal admission to intensive care or high dependency unit

6. Severe hypertension (defined as systolic BP $\geq 160 \text{ mm Hg}$ and/or diastolic BP $\geq 110 \text{ mm Hg}$, on

at least one occasion)

7. Caesarean section (any)

8. Labour onset, classified as spontaneous, induced, or no labour. (Spontaneous rupture of membranes without labour will be considered as spontaneous labour onset)

9. Maternal admission to intensive care or high dependency unit

10. Total number of nights in hospital

11. Gestational age at delivery

12. Stillbirth

13. Birthweight <3rd, <5th and <10th percentile for gestational age, calculated using the Fetal Medicine Foundation birthweight chart

14. Neonatal death (after birth or within the first 28 days of life)

15. Admission to neonatal care unit (for any duration)

16. Neonatal morbidity:

16.1. Intraventricular haemorrhage grade II or above, defined as bleeding into the ventricles

16.2. Neonatal sepsis (defined as confirmed bacteraemia in cultures)

16.3. Encephalopathy grade (mild, moderate, severe) requiring head cooling

16.4. Neonatal seizures

16.5. Anaemia defined as low haemoglobin and/or haematocrit requiring blood transfusion

16.6. Respiratory distress syndrome, defined as the need for ventilation with or without surfactant

16.7. Necrotising enterocolitis requiring surgical intervention

16.8. Composite of any of the above

17. Neonatal therapy:

17.1. Neonatal intensive care unit admission

17.2. Ventilation, defined as the need for positive pressure (continuous positive airway pressure) or nasal continuous positive airway pressure (NCPAP) or intubation

17.3. Composite of any of the above

Overall study start date

18/10/2022

Completion date

21/11/2024

Eligibility

Key inclusion criteria

1. Singleton pregnancy

2. Live fetus at 35+0-36+6 weeks' gestation

3. Able to provide informed and documented consent

Participant type(s)

Patient

Age group

Adult

Lower age limit

16 Years

Sex

Female

Target number of participants

4000-8000

Key exclusion criteria

1. Age <16 years
2. Women with established PE
3. Known major fetal abnormality
4. Participating in another intervention study that influences the outcomes of this study

Date of first enrolment

30/04/2023

Date of final enrolment

21/11/2024

Locations

Countries of recruitment

England

United Kingdom

Study participating centre

King's College Hospital

16-20 Windsor Walk

London

United Kingdom

SE5 8BB

Study participating centre

Medway Maritime Hospital Laboratory

Medway Maritime Hospital

Windmill Road

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Sponsor information

Organisation

King's College Hospital NHS Foundation Trust

Sponsor details

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Sponsor type

Hospital/treatment centre

Website

<https://www.kch.nhs.uk/>

ROR

<https://ror.org/01n0k5m85>

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 a high-impact peer-reviewed journal

Intention to publish date

01/11/2025

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?
Protocol article		10/04/2025	14/04/2025	Yes	No