

# Pregnancy outcome prediction study 2

<b>Submission date</b> 26/09/2019	<b>Recruitment status</b> Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 07/10/2019	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 22/11/2024	<b>Condition category</b> 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

Screening for pregnancy complications around delivery has not changed very much over the last 30 years. Moreover, we know that the methods currently employed, such as measuring the size of the “bump” with a tape measure, do not perform well

The aims of this trial are:

1. To determine whether a new approach, using ultrasound and blood tests, is effective at picking up high risk pregnancies, and
2. Whether intervening in the pregnancy, based on the result, reduces the risk. Intervention will consist primarily of the offer of earlier delivery by induction of labour

### Who can participate?

Women with a singleton pregnancy at the time of their dating ultrasound scan who have not had any previous births

### What does the study involve?

We will obtain blood at around 12, 20, 28 and 36 weeks of gestation from the women and blood from the father of the baby (if present and consents) at one of these visits. We will also obtain samples at the time of birth, including placenta, membranes and blood from the umbilical cord. We will collect data from the participants through a questionnaire and by performing ultrasound scans at around 20, 28 and 36 weeks. We will link the research data to the woman's and baby's clinical records. The data and biological samples will provide a resource to develop and validate predictive tests for adverse pregnancy outcome. However, in addition to this, we will also perform a randomised controlled trial. Using data from the Pregnancy Outcome Prediction study, we have developed a test which identifies women at high risk of complications at around eight months of pregnancy (36 weeks). The blood sample, scan information and mother's characteristics will be used to identify women at high risk following the 36 week visit. These women will be randomised to have routine care (meaning that the high risk status will not be revealed) or to have the result revealed with the offer of intervention, principally, early delivery of the baby by induction of labour. The primary outcome of the trial is a composite of either preeclampsia (a pregnancy-specific complication resulting in high blood pressure and other problems) in the mother or growth restriction of the baby

What are the possible benefits and risks of participating?

Participating involves some additional blood tests and these can cause mild discomfort and bruising. One benefit of participating is that we will reveal some scan information when it shows that there is a major problem. For example all women in the study will be told if their baby is in a breech presentation at 36 weeks. This allows time to try and turn the baby or to plan a caesarean delivery. In relation to the women who screen high risk, those who are randomised to having the result revealed and receiving intervention may either experience risks or benefits. We do not know the balance and this is the reason for doing the research. Women who screen high risk where the result is incorrect (i.e. they would have had a normal outcome if left alone) may experience an unnecessary intervention, specifically early induction of labour. However, women who screen high risk where the result is correct may benefit by avoiding complications of pregnancy through earlier delivery, before the complication can happen

Where is the study run from?

The Rosie Hospital, UK

When is the study starting and how long is it expected to run for?

January 2020 to June 2027

Who is funding the study?

Wellcome Trust, UK

Who is the main contact?

Prof. Gordon Smith

gcss2@cam.ac.uk

### **Study website**

<https://www.obgyn.cam.ac.uk/research/pops-2/pops2/>

## **Contact information**

### **Type(s)**

Scientific

### **Contact name**

Prof Gordon Smith

### **ORCID ID**

<http://orcid.org/0000-0003-2124-0997>

### **Contact details**

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# Additional identifiers

## EudraCT/CTIS number

Nil known

## IRAS number

271826

## ClinicalTrials.gov number

Nil known

## Secondary identifying numbers

215524/Z/19/Z, IRAS 271826

# Study information

## Scientific Title

The evaluation and development of novel diagnostic methods to understand and prevent placentally-related complications of human pregnancy

## Acronym

POPS2

## Study objectives

1. Screening nulliparous pregnant women using measurement of sFLT1/PlGF ratio at ~36 weeks of gestational age (wkGA) identifies women at increased risk of placentally-related complications at term
2. Revealing the result of screening using the sFLT1/PlGF ratio at ~36wkGA reduces the risk of maternal and perinatal morbidity and mortality
3. Measurement of other biomarkers in maternal blood may enhance risk prediction of placentally-related complications of pregnancy

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Approved 23/12/2019, East of England - Essex Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 1048106; NRESCommittee. EastofEngland-Essex@nhs.net), ref: 19/EE/0331

## Study design

Prospective cohort study with nested randomised controlled trial of screening and intervention

## Primary study design

Interventional

## Secondary study design

Randomised controlled trial

## Study setting(s)

Hospital

## **Study type(s)**

Screening

## **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 and fetal growth restriction

## **Interventions**

Women will be recruited at their dating ultrasound scan, typically performed ~12wkGA. Blood will be obtained at this visit, at their anomaly scan (20wkGA), and at two research appointments (28wkGA and 36wkGA) when research ultrasound scans will be performed. At the 36wkGA visit, women will be consented for participation in the RCT element of the study. For those who consent, their risk of term preeclampsia and/or fetal growth restriction will be calculated using a rule derived from the original POP study and based around the sFLT1/PLGF ratio. Women who screen high risk will then be randomly allocated to either having the result revealed or masked. Where the result is masked, there will be no communication of the risk score with the participant and she will continue to receive the standard of care at the Rosie Hospital. Women who screen high risk and are randomised to intervention will be reviewed and their results discussed. They will be offered early delivery, typically induction of labour between 37wkGA and 39wkGA where the clinical management of induction will follow the standard hospital protocols for high risk women.

Both arms will be followed up until the mother is discharged following the hospital admission when she delivered. Randomisation will be with minimisation based on the four elements of the screening assessment.

### **Randomisation:**

The randomisation list will be computer-generated by an independent statistician and provided for incorporation into the study database by the data manager

## **Intervention Type**

Mixed

## **Primary outcome measure**

The primary outcome is a composite, namely, one or more of the following:

1. Diagnosis of preeclampsia (using the ACOG 2013 definition),
2. Perinatal death or perinatal morbidity, or
3. Delivery of an infant with a birth weight <3rd percentile for sex and gestational age

Perinatal death will be defined as stillbirth or neonatal death. Perinatal morbidity is defined as  $\geq 1$  of the following: a 5 minute Apgar score <7, delivery with metabolic acidosis (defined as a umbilical cord artery or vein pH <7.1 and a base deficit of >10mmol/L) or admission to the neonatal unit (defined as admission <48 hours after birth and discharge  $\geq 48$  hours after admission). We will also study a subgroup of the primary outcome, namely, composite severe adverse outcome. This will be defined as one or more of the following: (i) preeclampsia with severe features (ACOG 2013 definition) (ii) perinatal death or severe perinatal morbidity. Severe

perinatal morbidity will be defined as livebirth associated with hypoxic ischaemic encephalopathy (any grade), use of inotropes, mechanical ventilation, or severe metabolic acidosis (defined as a umbilical cord artery or vein pH <7.0 and a base deficit of >12mmol/L).

### **Secondary outcome measures**

Secondary outcomes will include each of the individual elements of the maternal and perinatal composite described above. The following additional secondary outcomes will be studied:

#### **1. Maternal:**

- 1.1 Maternal death
- 1.2 Maternal stroke
- 1.3 Maternal admission to any medical unit (e.g. intensive care unit, stroke unit, coronary care unit, neurosciences critical care unit)
- 1.4 Placental abruption
- 1.5 Cord prolapse
- 1.6 Caesarean section
- 1.7 Epidural anaesthesia
- 1.8 Instrumental vaginal delivery
- 1.9 General anaesthesia
- 1.10 Post-partum haemorrhage (any >500ml)
- 1.11 Post-partum haemorrhage requiring blood transfusion
- 1.12 Infection (pyrexia >38°C and treated with a course of antibiotics)

Maternal death, stroke, admission to a medical unit, hemorrhage and infection will include all episodes occurring prior to discharge home following the delivery.

#### **2. Perinatal:**

- 2.1 Apgar at 1 minute
- 2.2 Apgar at 5 minutes
- 2.3 Apgar at 10 minutes
- 2.4 Umbilical arterial pH and base deficit
- 2.5 Umbilical vein pH and base deficit
- 2.6 Any/duration of admission to Special Care
- 2.7 Any/duration of admission to Neonatal Intensive Care
- 2.8 Fracture (any)
- 2.9 Seizures (any)
- 2.10 Prolonged hypotonia (>2h)
- 2.11 Abnormal level of consciousness (hyperalert, drowsy, lethargic, stupor, decreased response to pain, coma)
- 2.12 Tube feeding (any duration)
- 2.13 Head cooling
- 2.14 Phototherapy
- 2.15 Severe hypoglycemia (defined as requiring parenteral treatment or drug therapy)

### **Overall study start date**

10/05/2018

### **Completion date**

30/06/2027

## **Eligibility**

### **Key inclusion criteria**

1. Nulliparous (no previous births >23wkGA)
2. Single viable fetus at the dating ultrasound scan with an ultrasonic estimated gestational age <18wkGA

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Female

**Target number of participants**

13,664 (cohort recruits, fathers and RCT consents)

**Key exclusion criteria**

Does not meet inclusion criteria

**Date of first enrolment**

01/01/2020

**Date of final enrolment**

30/11/2026

**Locations****Countries of recruitment**

England

United Kingdom

**Study participating centre**

**The Rosie Hospital**

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Cambridge

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**Sponsor information****Organisation**

Cambridge University Hospitals NHS Foundation Trust

**Sponsor details**

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**Sponsor type**

Hospital/treatment centre

**Website**

<https://www.cuh.nhs.uk/research-and-development>

**ROR**

<https://ror.org/04v54gj93>

**Organisation**

Cambridge University

**Sponsor details**

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**Sponsor type**

University/education

**Website**

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**Funder(s)**

**Funder type**

Charity

**Funder Name**

Wellcome Trust

**Alternative Name(s)****Funding Body Type**

Private sector organisation

**Funding Body Subtype**

International organizations

**Location**

United Kingdom

## Results and Publications

**Publication and dissemination plan**

The primary publication arising from the study will report the primary and secondary outcomes of the trial comparing three groups:

1. Women who screened low risk
2. Women who screened high risk but were randomized to routine care, and
3. Women who screened high risk and were randomized to having the result revealed with the offer of intervention

Further publications will arise from the analysis of the study cohort

**Intention to publish date**

01/09/2027

**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

**IPD sharing plan summary**

Available on request

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No