ISRCTN45433810 https://doi.org/10.1186/ISRCTN45433810

Investigating blood vessel changes in the eye as a possible marker of pregnancy complications

Submission date
30/01/2024

Recruitment status
No longer recruiting

Registration date
25/03/2024

Overall study status
Ongoing

Last Edited
14/11/2025

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study aims to further our understanding of why pregnancy complications, including pre-eclampsia, fetal growth restriction and stillbirth, develop. Women at risk of these problems are currently identified using blood tests, ultrasound scans and blood pressure measurements; however, these assessments do not provide a complete picture. During pregnancy, there are dramatic changes in the structure and function of blood vessels throughout the body. The research team is currently conducting a study (I-TEST) to investigate whether taking pictures of blood vessels in the back of the eye using specialised cameras (retinal imaging) can reveal changes linked to the development of pregnancy complications. In this new study (I-TEST-M), the team will gather additional information using simple, quick, non-invasive tests which measure blood flows and the "stiffness" of blood vessels at different locations throughout the body. This will help to understand how structural changes in the blood vessels in the back of the eye are related to changes in blood vessels elsewhere. It will also indicate whether monitoring changes in blood vessels and flows could be a new way of identifying and monitoring those at risk of pregnancy complications.

Who can participate?
Pregnant women aged between 16 and 50 years old who are already participating in the I-TEST study.

What does the study involve?
Participants will be invited to study visits either at fortnightly intervals in late pregnancy (after 34 weeks), or at three time points in pregnancy (around 12, 28 and 36 weeks) and 6 weeks after birth. At these visits, tests to measure blood flow and blood vessel "stiffness" will be carried out at different locations throughout the body. They will also be asked to provide a urine sample at each study visit so that we can measure levels of protein in the urine.

What are the possible benefits and risks of participating?
There will be no direct benefits from taking part in the study, but our results may help to improve the healthcare of pregnant women in the future. None of the measurements taken are expected to pose any risks to the health of participants or their pregnancies. However, there may be inconvenience associated with having to take time to travel to and attend study visits.

There is a small possibility that the measurements may reveal a health problem that a participant was unaware of. In the unlikely scenario that this does occur, the participant will be referred to receive further medical advice and treatment as appropriate.

Where is the study run from?
The University of Edinburgh

When is the study starting and how long is it expected to run for?
January 2024 to August 2026

Who is funding the study?
The British Heart Foundation (BHF)

Who is the main contact?
Dr Kathryn Hunt (Clinical Research Fellow), khunt2@ed.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
IRAS 339302

ClinicalTrials.gov (NCT)
Nil known

Study information

Scientific Title
I-TEST-M: modelling retina-placental interactions in pregnancy

Acronym
I-TEST-M

Study objectives
This study aims to identify and test novel biomarkers relating to the retinal vascular, ophthalmic artery and systemic circulatory blood flows, for early detection of pregnancy complications and integration into models that predict pre-eclampsia, fetal growth restriction and stillbirth. A computational modelling approach will be used to simulate blood flows within the maternal circulation and investigate the relationship between changes in the retinal and uteroplacental circulations during normal pregnancies and those affected by vascular dysfunction. This approach will complement that of the I-TEST study, which aims to develop retinal imaging-derived biomarkers of placental dysfunction and within which our sub-study is nested, by relating structural changes to physiological adaptation of the entire maternal circulation.

It is hypothesised that retinal vascular changes reflect the dynamic remodelling of maternal systemic and uteroplacental circulations during pregnancy. This approach will complement that of the I-TEST study, which aims to develop retinal imaging-derived biomarkers of placental dysfunction and within which our sub-study is nested, by relating structural changes in retinal vessels to physiological adaptation throughout the wider maternal circulation.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 19/03/2024, London - Brighton & Sussex Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8140; brightonandsussex.rec@hra.nhs.uk), ref: 24/LO/0218

Study design
Single-centre two-phase observational study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Vascular dysfunction in pregnancy (manifesting as pre-eclampsia, fetal growth restriction, or stillbirth)

Interventions
This is a single-centre observational study with two phases as follows:
- A longitudinal case-control study carried out during late pregnancy
- A longitudinal cohort study from 12 weeks gestation until 6 weeks postnatal

This study is nested within the I-TEST study, through which participants will undergo serial multimodal retinal imaging in pregnancy, between 12 and 36 weeks gestation.

The following datasets will be collected at study visits. In phase one, these will be at fortnightly intervals from 34 weeks gestation until birth. In phase two, these will be at 12, 28 and 36 weeks gestation and 6 weeks postnatally, with additional (up to fortnightly) study visits offered for women with diagnosed pre-eclampsia or fetal growth restriction.

Maternal physiological data:
• Maternal height will be measured.

Maternal cardiovascular data:
• Heart rate and systolic and diastolic blood pressure will be measured lying, sitting and standing.
• Echocardiography and electrocardiography (ECG) cardio-impedance will be conducted for measurement of cardiac output and aortic size.
• Pulse wave velocity: aortic central pulse wave velocity will be assessed with a tonometry-based device placed sequentially over the carotid and femoral artery in conjunction with simultaneous ECG recording. Peripheral pulse wave velocity will then be assessed with a tonometry-based device placed sequentially over either the carotid and radial arteries, or femoral and popliteal /tibial arteries, in conjunction with simultaneous ECG recording. The distance between points of pulse wave detection will be measured manually to allow the calculation of central and peripheral pulse wave velocities.

Ultrasound assessment:
• Maternal uterine artery Doppler measurements will be made and the pulsatility index from both uterine arteries will be recorded.
• Maternal ophthalmic artery Doppler measurements will be made, with waveforms obtained in sequence from the right eye, left eye, and again right and then left eye. The following four indices will be recorded: first peak systolic velocity, second peak systolic velocity, pulsatility index, and the ratio of second to first peak systolic velocities.
• Maternal middle cerebral artery Doppler measurements will be made and the pulsatility index from both middle cerebral arteries will be recorded.

Biological samples:
• At each study visit during phase two, we will collect a urine sample for analysis of proteinuria (albumin-creatinine ratio).

In addition to the serial retinal imaging carried out by I-TEST, participants recruited to phase two of I-TEST-M will undergo additional retinal imaging (fundal photography, optical coherence tomography, and optical coherence tomography angiography) at the 6-week postnatal study visit.

Intervention Type
Other

Primary outcome(s)
The following non-invasive cardiovascular and ultrasound Doppler blood flow outcome variables will be measured, in women enrolled in the I-TEST study, either at fortnightly intervals in late pregnancy (after 34 weeks) until birth for the case-control arm of the study (phase one), or at three-time points in pregnancy (around 12, 28 and 36 weeks) and 6 weeks postnatal for the longitudinal cohort arm of the study (phase two).

Maternal cardiovascular data:
1. Heart rate, systolic and diastolic blood pressure measured using a sphygmomanometer in lying, sitting, and standing positions
2. Cardiac output +/- aortic size measured using electrocardiography (ECG) cardio-impedance or echocardiography.
3. Pulse wave velocity, including aortic central pulse wave velocity and peripheral pulse wave velocity, measured over different arterial segments using a tonometry-based device with simultaneous ECG recording

Doppler ultrasound blood flow assessments:
1. Maternal uterine artery blood flow, including the pulsatility index from both uterine arteries
2. Maternal ophthalmic artery blood flow, including four indices: first peak systolic velocity, second peak systolic velocity, pulsatility index, and the ratio of second to first peak systolic velocities
3. Maternal middle cerebral artery blood flow, including the pulsatility index from both middle cerebral arteries

Key secondary outcome(s))
Resistance of the retinal and uteroplacental vascular beds, as predicted by personalised computational cardiovascular models, will be assessed either at fortnightly intervals in late pregnancy (after 34 weeks) until birth for the case-control arm of the study (phase one), or at three-time points in pregnancy (around 12, 28 and 36 weeks) and 6 weeks postnatal for the longitudinal cohort arm of the study (phase two). These will be generated using the cardiovascular data as described in the primary outcome measures, which will be used to parametrise distinct cardiovascular model simulations relating to each specific gestational /postnatal time points.

For the longitudinal cohort arm of the study (phase two), proteinuria will be assessed as an albumin-creatinine ratio measured using immunoturbidimetry, at three time points in pregnancy (around 12, 28 and 36 weeks) and 6 weeks postnatally.

Clinical outcome data will be collected postnatally from the medical record for all participants, at least two weeks following birth. These will relate to the occurrence of pregnancy complications and birth outcomes, including birthweight, gestation at birth, mode of birth, indication for delivery, neonatal unit admission, respiratory distress, Apgar scores and umbilical cord pH levels. Collection of clinical outcome data will allow us to use the collected cardiovascular measures, and outputs from computational simulations, in predictive outcome modelling for pregnancy complications.

Completion date
01/08/2026

Eligibility

Key inclusion criteria
1. Enrolled in I-TEST
2. Age 16-50 years old
3. Able to give informed consent
4. Singleton non-anomalous viable pregnancy
5. Living in Lothian area

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Upper age limit
50 years

Sex
Female

Total final enrolment
0

Key exclusion criteria
1. Women who are not pregnant
2. Aged under 16 or over 50 years old
3. Women who are classified as Adults with Incapacity (AWI) as determined by midwife, GP or research team
4. Delivery indicated before 34 weeks (for phase one)
5. Multiple pregnancy
6. Diagnosed congenital anomaly

Date of first enrolment
01/05/2024

Date of final enrolment
01/01/2026

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road

Edinburgh
Scotland
EH16 4SA

Sponsor information

Organisation
Accord (United Kingdom)

ROR
https://ror.org/01x6s1m65

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository (University of Edinburgh DataStore).

This is a prospective study, and therefore informed participant consent will include provision for data sharing to maximise the value of the dataset for wider research use. The fully anonymised dataset will be available on study close-down with metadata documentation to enable understanding and reuse, upon request from Professor Rebecca Reynolds (email R.Reynolds@ed.

ac.uk). All data users will be required to agree to a set of terms for the use of the data, in writing, prior to receipt of the data.

IPD sharing plan summary

Available on request, Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.0	12/01/2024	02/02/2024	No	No
Protocol file	version 1.1	19/03/2024	22/03/2024	No	No
Study website			14/11/2025	No	No