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Understanding placental, heart and brain development using advanced MRI and ultrasound scans before birth

Submission date
29/08/2023

Recruitment status
Recruiting

Registration date
05/09/2024

Overall study status
Ongoing

Last Edited
08/10/2024

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
In the UK, more and more babies with congenital heart disease (CHD) are being diagnosed on prenatal ultrasound scans, meaning doctors can plan to give them the treatment they need as soon as they are born. However, many forms of CHD, particularly those affecting the left side of the heart, have been linked with problems in the baby's placenta, for reasons that aren't clear. Similarly, babies who are known to have placental problems can have changes on prenatal scans that look very similar to left-sided CHD. These babies can also be at increased risk of other heart-related problems - such as high blood pressure, heart attacks and strokes - in later life.

In this study, women carrying a baby suspected to have left-sided CHD will be asked to attend for additional 3D ultrasound and MRI scans, to help us understand more about how the function of placenta is related to the development of the baby’s heart and blood vessels.

Our hope is that this information could help us to diagnose some forms of CHD more accurately, as well as help to understand more about how a baby’s environment before birth might shape their future cardiovascular health.

Who can participate?
Women aged 18 years or older, with a pregnancy at 18 weeks or later at the time of scan

What does the study involve?
The study involves inviting participants to undergo one to two outpatient antenatal ultrasound scans and/or one to two outpatient MRI scans (without general anesthesia) during pregnancy. Oxygen via facemask might be offered during scans and will be discontinued after imaging. Each scan lasts up to 60 minutes per patient. Some women might receive an MRI compatible Doppler device for fetal heart rate measurement. Certain parameters will be assessed before and after oxygen administration. After the scans, participants will return home following standard procedures.

Participants will receive an information sheet and can ask questions before deciding. They can also view an MRI scanner beforehand and watch a video explaining the fetal MRI process. Consent for scans can be obtained from various study personnel experienced in the process.

MRI and ultrasound scans can be performed in any order and may occur singly, up to twice each during pregnancy, provided criteria are met and consent is given.

After delivery, placenta collection for histological analysis will occur if specific consent is granted. The consent also allows collecting clinical outcome data for the pregnancy and baby, including postnatal diagnoses, treatments, and outpatient follow-ups. At one year of age, participants may opt for a follow-up research ultrasound scan for their baby, with enrollment requiring separate written consent. The study's postnatal arm includes a research clinic appointment at around 12 months, with an echocardiogram. Declining this doesn't affect regular care.

What are the possible benefits and risks of participating?
We hope that the information gained from the study will lead to better antenatal diagnosis of fetal abnormalities and be used in specialist antenatal clinics nationally.
Fetal ultrasound has no known risks, and there are no additional risks to your baby or long-term effects of having the MRI scan. Maternal oxygen has also been shown to be safe to pregnant women and their babies - even when given for much longer periods than we are doing in our study. There are some patients in whom care should be taken before giving oxygen, such as those undergoing active chemotherapy or those with severe chronic lung disease.

Where is the study run from?
1. Guy's and St Thomas' Hospitals (UK)
2. King's College Hospital (UK)

When is the study starting and how long is it expected to run for?
August 2023 to September 2027

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Dr David Lloyd, david.lloyd@kcl.ac.uk

Contact information

Type(s)
Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
320644

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 62529

Study information

Scientific Title
The placenta-cardiac imaging study

Acronym
PLACARD

Study objectives
Uteroplacental insufficiency is linked directly to the development of important cardiac abnormalities in fetal life, as well as early-onset vascular dysfunction and an increased risk of cardiovascular disease in later life.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 17/06/2024, West of Scotland REC5 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, United Kingdom; +44 141 314 0213; WoSREC5@ggc.scot.nhs.uk), ref: 24/WS/0051

Study design
Observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See outputs table

Health condition(s) or problem(s) studied
Mothers carrying a fetus with diagnosed with congenital heart disease and/or other congenital abnormalities
Mothers carrying a fetus with intrauterine growth restriction
Mothers with suspected placental pathology or insufficiency
Healthy pregnant women

Interventions
During pregnancy
Each participant will be invited to attend for between one and two out-patient antenatal ultrasound scans(s) and/or one to two outpatient MRI scan(s) (not under general anaesthetic). During each of these investigations the mother may be offered oxygen via facemask which will be stopped once imaging is complete. The maximum total scan time is 60 minutes (per patient per scan). For some women, a CE-marked MRI compatible Doppler device may also be used during the scan to allow for more accurate fetal heart rate measurement (Smart-sync®, North Medical GmbH, Hamburg). Some echocardiographic and MRI parameters will be repeated before and after administration of oxygen. Once completed, oxygen would be removed and the patient would return home, as per standard institutional protocol.

We will provide a written information sheet for participants to read. They will then be free to ask questions and been given time to decide. If participants wish to view the MRI scanner prior to consenting this can be arranged. In addition, we will refer these patients to the video created by the KCL Imaging Facility showing what happens from the beginning to the end of a fetal MR appointment. Consent for ultrasound scans and MR imaging can be obtained by any of the researchers and clinical staff involved in the study. They will have experience in obtaining consent and full knowledge of what the study entails.

Depending on patient circumstances, MRI or US may be performed singly and in any order. Up to two US and MRI scans may performed in any patient during pregnancy, provided inclusion criteria are met on both occasions and patient consent is obtained.

After the pregnancy ends
Immediately after the delivery, the placenta will be collected by a member of the research team and securely transferred for histological analysis (Amsterdam criteria), provided specific consent has been obtained. Consent in pregnancy as above will allow for collection of clinical outcome data regarding the pregnancy and the baby, for example data on postnatal diagnosis (including imaging), medical and/or surgical treatment (if any), and clinical data from subsequent outpatient appointments for mother and/or baby. After appropriate postnatal screening procedures (see below) the patient will be approached by the research team to offer a follow-up research ultrasound scan at one year of age for their baby. This study will be verbally explained again as needed, and another copy of the patient information sheet (physically or by email) will be offer which they can again take home to discuss with friends and family. They will have the

opportunity to ask any questions, and should they wish to participate, their baby will be formally enrolled in the postnatal arm of the study with a separate parent/guardian written consent. This will entail a formal research clinic appointment at the Evelina London Children's Hospital at around 12 months postnatal age, including a research echocardiogram. If the patient declines to enter their child into this arm of the study, they will be followed-up according to conventional clinical methods with no impact on their care.

No randomisation will be performed in this study.

Intervention Type
Other

Primary outcome measure
Characterise the baseline fetoplacental conditions associated with fetal cardiac development using novel fetal MRI/US methods, including response to maternal oxygenation, and their relationship to early cardiovascular health:
1. Placenta
1.1. Total placental volume (MRI): Deformable motion-correction software applied to standard T2-weighted images via a fully automated pipeline at 20-26 weeks and 30-36 weeks gestation
1.2. Functional placental volume: Partially localised quantitative T2* maps at 20-26 weeks and 30-36 weeks gestation
1.3. Uteroplacental flow: Uterine artery flow (QUTA) measured with PC-MRI at 20-26 weeks and 30-36 weeks gestation
1.4. Fetoplacental flow: Umbilical vein flow (QUV) measured with PC-MOG at 30-36 weeks gestation
1.5. Umbilical vein SaO2: T1/T2 mapping (see SickKids Toronto collaboration) at 30-36 weeks gestation
1.6. Fetal O2 delivery (DO2): Calculated as [QUV * UVO2] at 30-36 weeks gestation
1.7. Total placental volume (US): Automatic identification and segmentation from US data using a bespoke U-Net architecture at 20-26 weeks and 30-36 weeks gestation
1.8. Uteroplacental resistance: 2D pulsed-wave Doppler of the uterine artery at 20-26 weeks and 30-36 weeks gestation
1.9. Fetoplacental resistance: 2D pulsed-wave Doppler of the umbilical artery at 20-26 weeks and 30-36 weeks gestation
2. Heart
2.1. 3D whole-heart volumetry: Novel 3D + time volumes to allow for measurement of static ventricular volumes, stroke volumes and ejection fraction at 30-36 weeks gestation
2.2. Vascular flow measurements: PC-MOG with a recently developed a priori scoring system to improve reliability at 30-36 weeks gestation
2.3. 3D vascular reconstruction: Automated reconstruction via a 3D-UNet approach for robust localisation of the fetal thorax even in early gestation; processed via a non-rigid extension of previous methods for accurate visualisation of smaller vessels at 20-26 weeks and 30-36 weeks gestation
2.4. 3D vascular shape analysis: 3D computational modelling to allow for a more detailed and reproducible means of analysing aortic arch geometry at 20-26 weeks and 30-36 weeks gestation
2.5. Fetal intracardiac streaming/Pulse wave velocity: Novel "4D flow" sequences for time-resolved visualisation of 3D flow patterns and calculation of fetal pulse wave velocity using external Doppler cardiac gating (smart-sync) at 30-36 weeks gestation
2.6. 2D vascular measurements: Referenced to a cohort of >7000 patients at 20-26 weeks and 30-36 weeks gestation
2.7. 2D Doppler measurements: Standardised pulsed-wave analysis referenced to a cohort of

>7000 patients. PW Doppler of the branch pulmonary to infer changes in pulmonary vascular resistance with MHO2 at 20-26 weeks and 30-36 weeks gestation
2.8. 3D STIC structural imaging: 3D vascular data acquired using a GE Voluson system at 20-26 weeks and 30-36 weeks gestation
2.9. 3D STIC volumetric imaging: 3D volumetric data acquired using a GE Voluson system at 20-26 weeks and 30-36 weeks gestation
2.10. Myocardial deformation: Speckle tracking fetal echocardiography at 20-26 weeks and 30-36 weeks gestation
3. Brain
3.1. Total brain volume (MRI): Fully automated motion-corrected 3D brain volume at 20-26 weeks and 30-36 weeks gestation
3.2. Structural brain imaging: Including cortical gyrification and structural abnormalities at 20-26 weeks and 30-36 weeks gestation
3.3. Cerebral blood flow: Superior vena cava flow (QSVC) measured using PC-MOG and indexed to total brain volume at 20-26 weeks and 30-36 weeks gestation
3.4. Total brain volume (US): Using standard 3D US volume acquisition at 20-26 weeks and 30-36 weeks gestation
3.5. Cerebrovascular resistance & cerebroplacental ratio: Middle cerebral artery Doppler pulsatility index (/uterine artery pulsatility index) at 20-26 weeks and 30-36 weeks gestation
4. Postnatal cardiovascular assessment at 12 months of age is designed to be equivalent to a routine paediatric cardiology outpatient assessment. This will include baseline anthropometry and observations (systematic blood pressure measurement, heart rate, saturations, respiratory rate), followed by a standard paediatric echocardiogram to include measurements of the main cardiac structures and assessment of heart function, with the additional of ultrasound estimates arterial stiffness (pulse wave velocity).

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
30/08/2023

Completion date
30/09/2027

Eligibility

Key inclusion criteria
1. Women with a pregnancy at 18 weeks or later at the time of scan
2. Women that are 18 years of age and over
3. Women who can read the information sheet and understand the purpose of the study and what it would entail

Participant type(s)
Healthy volunteer, Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
300

Key exclusion criteria
All groups:
1. Maternal weight > 125kg
2. Maternal claustrophobia
3. Patients in the first trimester of pregnancy
4. Unable to give informed consent
5. Contra-indication to MRI

Healthy controls:
1. Fetal growth restriction
2. Fetal congenital anomaly
3. Maternal placental insufficiency

Date of first enrolment
01/10/2023

Date of final enrolment
30/09/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Guy's and St Thomas' Hospitals
Westminster Bridge Road
London
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SE1 7TH

Study participating centre
King's College Hospital
Denmark Hill
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SE5 9RS

Sponsor information

Organisation
King's College London

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Sponsor type
University/education

Website
http://www.kcl.ac.uk/index.aspx

ROR
https://ror.org/0220mzb33

Organisation
Guy's and St Thomas' NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
http://www.guysandstthomas.nhs.uk/Home.aspx

ROR
https://ror.org/00j161312

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

Publication and dissemination plan
The results of the study will be disseminated locally, nationally and internationally in relevant meetings and conferences. Academic papers will be published in journals associated with paediatric congenital heart disease and maternal and fetal health.

Intention to publish date
30/09/2028

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 (REDCap, King's College London School of BMEIS). Access via internal KCL IT, available 24/7 to registered users, consent obtained, data is anonymised (numerical identifier only), data will be used in line with protocol as approved by REC.

IPD sharing plan summary
Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Participant information sheet	Clinical group version 1.4	02/07/2024	10/07/2024	No	Yes
Participant information sheet	Control group version 1.4	02/07/2024	10/07/2024	No	Yes