

A study to improve our understanding of the genetic causes of swelling in babies before birth

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		<input type="checkbox"/> Protocol
Registration date 05/03/2020	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
Last Edited 25/08/2023	Condition category Pregnancy and Childbirth	<input type="checkbox"/> Individual participant data
		<input type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims

Fetal hydrops (FH), the abnormal accumulation of fluid in the fetus, is an important cause of fetal loss, with a perinatal mortality of approximately 60%. Rhesus incompatibility as a cause of immune FH, is now rare in the UK. The two most commonly affected systems giving rise to non-immune FH are cardiovascular (20%) and lymphatic (15%). In 20 %, the cause is still unknown. To better understand the aetiology of FH, a retrospective and prospective study of cases in five Fetal Medicine Centres will be undertaken.

Who can participate?

Individuals affected by fetal oedema or hydrops in-utero.

What does the study involve?

Accurate incidence statistics and sub-classification of FH by cause, according to strict inclusion /exclusion criteria, over 5 years will be produced. Analysis of genomic data from DNA submitted to e.g. the 100,000 Genomes Project will identify existing causal genes and discover novel gene candidates for FH. No additional visits or consultations are required to take part in this study.

What are the possible benefits and risks of participating?

This study will provide information which will help clinicians diagnose the cause of a baby's oedema and provide a better prognosis. In the future, we hope that accurate diagnostic information will be useful to those developing treatments for fetal oedma.

There are no disadvantages or risks of taking part other than that mentioned above momentary discomfort at the site of blood sampling where applicable. The disadvantages of genetic testing such as the potential to find variants of unknown significance and participants and their doctors will be notified of incidental findings.

Where is the study run from?

1. King's College Hospital (UK)
2. St George's Hospital (UK)
3. University College London Hospital (UK)
4. Queen Charlotte's and Chelsea Hospital (UK)
5. Southampton General Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2019 to July 2022

Who is funding the study?

1. British Heart Foundation (BHF) (UK)
2. National Institute for Health Research (NIHR) (UK)

Who is the main contact?

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Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

Integrated Research Application System (IRAS)

259711

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number

CPMS 41101, IRAS 259711

Study information

Scientific Title

An Investigation into the aetiology and genetics of fetal oedema/hydrops with a focus on lymphatic related hydrops

Acronym

FOLD

Study objectives

1. There are ultrasound features which are predictive of genetic aetiology of fetal hydrops.
2. Many of the undiagnosed cases have mutations in genes associated with aberrant lymphatic development.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 29/03/2019, East Midlands - Derby Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; ; NRESCCommittee.EastMidlands-Derby@nhs.net), ref: 19/EM/0038

Study design

Non-randomized cohort study

Primary study design

Observational

Study type(s)

Diagnostic

Health condition(s) or problem(s) studied

Fetal oedema/hydrops with a focus on lymphatic related hydrops

Interventions

PART 1- RETROSPECTIVE AETIOLOGY Study (AIM 1)

Three years' worth of retrospective data regarding all pregnancies meeting the inclusion criteria will be gathered from the five collaborating fetal medicine centres. For a further two years after starting this study these centres will be visited at regular intervals (predicted to be six-monthly) to gather the most recent cases. In total five years' worth of data will be gathered.

Information will be gathered and stored anonymously and will include: maternal and family medical history, mode of conception and pregnancy history, pregnancy investigations, birth and early neonatal history.

Ultrasound features will also be collected (where available) including information about fetal and maternal anatomy and measurements and any indicators of abnormality in the baby.

The researchers will use statistical analysis to look for relationships between specific findings on the ultrasound scans/ features of the history and the various causes of fetal hydrops.

PART 2 – PROSPECTIVE PREGNANCY FOLLOW-UP (AIM 2)

Those patients, meeting the inclusion criteria, being seen for their routine NHS care at King's College Hospital or St George's Hospital fetal medicine departments during the course of this study will be invited to participate in our study.

Participation will be explained to the patient verbally as well as in writing. In addition, the researchers will invite the participant to follow up after conclusion of the pregnancy.

The researchers will ask patients for their consent to follow up the progress and document the course of the fetal hydrops during the course of the pregnancy. The researchers may ask them for permission to look at additional ultrasound features during their next NHS scan. These are most likely to be the sort of measurements that are part of routine ultrasound examination but it might be that the particular measurement is not normally taken at that time or for that particular problem.

Additional ultrasound measurements may add a few extra minutes to the time taken for their routine ultrasound scan but would not be anticipated to cause any discomfort or distress. Ultrasound is considered a safe investigation in pregnancy and no harm would result to the fetus. The results and interpretation of any additional measurements would be explained to the woman/couple as desired.

No invasive procedures or investigations will be requested of, or offered, to pregnant women for the purposes of this study. The measurements will be taken at their routine ultrasound appointment at all times. No additional ultrasound appointment will need to be booked for the purpose of this study.

For those pregnancies, which end via termination or when a baby dies in the womb, the researchers will request to analyse post-mortem reports, images and investigations (including exome/genome data). For those pregnancies, which continue to livebirth, the researchers will collect data regarding the baby's condition at birth. The researchers will document the results of their examination and medical investigations and interventions in the neonatal and infant period (requesting access to medical records). The researchers will follow up on liveborn infants at three months, six months and one year by way of telephone questionnaire with the parents. The telephone interview will ask the parents for the following.

- 1) An update on the child's medical condition since our last contact (to include current medical state, new diagnoses, investigations reported or pending and interventions (therapeutic, surgical or pharmacological).
- 2) A brief enquiry regarding age-appropriate milestone attainment and parental concerns around development.

Should any unaddressed medical or developmental concerns arise during the period of the follow-up, consent will be requested to contact the child's GP and/or health visitor. In the unlikely scenario that a conversation with a parent suggests that a child needs urgent medical assessment, the researchers will help the parents to access urgent GP or paediatric review or direct them towards accident and emergency (and provide covering letter documenting concerns).

Before any contact is made, every attempt will be made to ensure that the child has not passed away since our last contact. This may involve accessing the child's electronic hospital records or calling the GP practice.

PART 3 - GENOMICS OF FETAL OEDEMA (AIMS 3 & 4)

Genomic data will be gathered from a number of different sources:

1. Those pregnancies meeting inclusion criteria who undergo genomic testing at St. George's Hospital or King's College Hospital. The researchers aim to recruit these patients to this study and, where consent is provided, the researchers will re-analyse the genomic data from those pregnancies where no cause could be identified
2. Sequence data will be made available from genetic centres throughout the UK who access genomic testing via nationally organised genomic testing initiatives. The nationalised testing process will create data sets containing only the data from patients, who have consented to research. This data will be made available to relevant research groups. The researchers will have access to this data through our membership of the Paediatric and the Cardiovascular GeCIPs (certified research group) of the 100,000 Genomes Project
3. The researchers have stored sequence information from patients who have undergone NHS genomic testing in whom no causal mutation has been found. All of these patients have consented for NHS genomic testing and the researchers will access the data of those who have consented to involvement in research
4. The researchers have stored DNA from patients who have been clinically reviewed in the past and in whom single-gene (or small panel) testing proved uninformative. Some of these samples are historical and will not have given informed consent for genomic testing (which did not exist at that point). The researchers will write to the patients and provide information about this

study. Those wishing to participate will be taken through the consenting process
5. Patients may be identified in the Lymphoedema outpatient clinic (as they presented with features meeting the inclusion criteria whilst still in the womb). These patients will be provided with information and an opportunity to discuss the study and asked for consent for exome sequencing

A small number of patients may be asked to provide a blood sample where the researchers do not already have DNA stored (or it is of insufficient quality/quantity) or they have not already undergone NHS genomic testing.

Genomic data will be re-analysed to identify variants that the researchers believe to be related to the phenotype. The researchers will also use the data to identify new genes associated with the phenotype. Where the researchers believe the researchers have identified a causal mutation this will be confirmed by Sanger sequencing in Dr Pia Ostergaard's research lab, St George's, University London. These results will be returned to the referring clinician who would be expected to have them confirmed in an NHS accredited laboratory before being returned to the patient (if this is what the patient requested on the written consent form).

No mutations in genes other than those associated with the phenotype will be reported (i.e. no incidental findings are acted on). Only mutations deemed likely pathogenic or pathogenic according to the American College of Medical Genetics will be reported (no variants of unknown significance, VUS, will be reported). These points will be explained to the patient during the consenting process.

Intervention Type

Other

Primary outcome(s)

Part 1. Measurement of various indices from an ultrasound examination of affected pregnancy
Part 2. Information regarding fetal outcome/ child health and development, via a telephone interview with parents, at one year in children with a specific genotype
Part 3. Identification of sequence variants from genomic data sets

Key secondary outcome(s)

none

Completion date

31/07/2022

Eligibility

Key inclusion criteria

1. All cases of fetal hydrops at any gestation (as defined by the abnormal accumulation of fluid in two or more fetal compartments)
2. All cases of single compartment oedema (the abnormal accumulation of fluid within a fetal body cavity, for example, ascites, isolated hydrothoraces, generalised skin oedema)
3. Fetuses with a Nuchal Translucency (NT) >4.5mm at the 12/40 ultrasound scan.
4. Individuals affected by fetal oedema or hydrops in-utero for whom no explanation has been identified

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Sex

All

Key exclusion criteria

Pregnancies with evidence of Rh or other blood group incompatibility (immune hydrops)

Date of first enrolment

27/07/2019

Date of final enrolment

01/10/2021

Locations

Countries of recruitment

United Kingdom

England

Study participating centre

King's College Hospital

King's College Hospital NHS Foundation Trust

Denmark Hill

London

United Kingdom

SE5 9RS

Study participating centre

St George's Hospital

St George's University Hospitals NHS Foundation Trust

Blackshaw Road

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SW17 0QT

Study participating centre

University College London Hospital

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Study participating centre**Queen Charlotte's and Chelsea Hospital**

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Study participating centre**Southampton General Hospital**

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Sponsor information

Organisation

St George's University Hospitals NHS Foundation Trust

ROR

<https://ror.org/039zedc16>

Funder(s)

Funder type

Charity

Funder Name

British Heart Foundation; Grant Codes: FS/18/79/33932

Alternative Name(s)

The British Heart Foundation, the_bhf, BHF

Funding Body Type

Private sector organisation

Funding Body Subtype

Trusts, charities, foundations (both public and private)

Location

United Kingdom

Funder Name

National Institute for Health Research (NIHR) (UK)

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

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 not expected to be made available due to the rarity of the conditions involved makes it very difficult to de-identify information sufficiently for the public domain. Specific data sets required to authenticate accuracy of results will be provided in results publications

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version v4	16/04/2019	05/03/2020	No	Yes