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FERN: Intervention or expectant management for early onset selective fetal growth restriction in monochorionic twin pregnancy

Submission date
11/08/2023

Recruitment status
No longer recruiting

Registration date
15/08/2023

Overall study status
Completed

Last Edited
25/07/2025

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims

The UK has approximately 11,000 twin pregnancies per year with a third of these sharing a placenta (the afterbirth), called monochorionic (MC) twins. MC twin pregnancy poses extra risks to both the mother and her babies, with some babies dying during pregnancy or shortly after birth. Often this can be due to complications of MC twin pregnancy such as selective fetal growth restriction (sFGR) where one twin is smaller than the other or twin-to-twin transfusion syndrome. sFGR affects one in seven MC twin pregnancies in the UK although less is known about pregnancies where this happens early (before 24 weeks of pregnancy). sFGR in MC twins poses some unique risks; if the smaller twin dies, its death may harm the other twin, causing either death or brain damage. There are three main ways of managing twin pregnancies with sFGR. Firstly, a watch-and-wait approach (also called expectant management). The difficulty with this approach is that the smaller twin could die in the womb, which can lead to death or brain damage to the other twin. Secondly, a procedure can be performed which blocks the umbilical cord from the smaller twin to the placenta and as a consequence, the smaller twin dies (also known as selective termination). This allows the larger twin to continue growing and gain maturity, hopefully delivering at a normal gestation. Finally, a laser can be used to completely separate the twins' circulations. This method protects the larger twin in the event of the death of the smaller twin but increases the risk of losing the smaller twin. There is no good evidence on the best way of managing sFGR in twin pregnancies, so women and their partners are offered different management options depending on where they live and who they see. It is also clear that there are gaps in what is known about sFGR. A UK national registry of complicated twin pregnancies has already been set up to collect information about pregnancy outcomes. However, there is an urgent need for more research to see if a study comparing different management options is possible. Before running such a study, understanding is needed about things like how many twin pregnancies would be needed to run the study and whether women and clinicians would be willing to take part. Which management options will work best and what outcomes are important also need to be researched.

Who can participate?
Adults having an MC twin pregnancy and diagnosed with sFGR (WP1), parents and clinicians (WP2) and parents, clinicians and patient groups (WP3)

What does the study involve?
Three work packages (WP) will be undertaken to help the team to define the current situation and design a future study that will inform how best to manage sFGR in MC twins.

In WP1, women (100) with sFGR in MC twin pregnancies will be recruited in 23 UK fetal medicine units over 18 months.

In WP2, interviews with parents (25) and doctors (25) will be performed to get their views about whether a bigger trial is possible and what the different types of management should be.

WP3 will develop a consensus about what is most important by seeking agreement between clinicians, parents, patient groups and funders to design the best possible study to answer the 'What is the best way to manage MC twin pregnancies with sFGR?'.

What are the possible benefits and risks of participating?
The study is anticipated to determine the current UK practice and number of cases/year, the natural history of sFGR in MC twins, pregnancy outcomes, women's preference, clinicians' preference, ethical dilemmas, whether it is feasible to conduct a trial of active intervention versus expectant management in sFGR in MC twins and the key elements of a potential future trial design.
There are no risks taking part in this study.

Where is the study run from?
Harris Wellbeing Research Centre, University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
December 2017 to November 2025

Who is funding the study?
National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (UK)

Who is the main contact?
fern1@liverpool.ac.uk (UK)

Contact information

Type(s)
Public

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Additional identifiers

Integrated Research Application System (IRAS)
286337

Central Portfolio Management System (CPMS)
47201

Study information

Scientific Title
FERN: Intervention or expectant management for early onset selective fetal growth restriction in monochorionic twin pregnancy

Acronym
FERN

Study objectives
To assess the feasibility of conducting a randomised controlled trial (RCT) of active intervention versus expectant management in monochorionic (MC) twin pregnancies with early-onset (prior to 24 weeks) selective fetal growth restriction (sFGR)

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 04/12/2020, South West - Cornwall and Plymouth Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, United Kingdom; +44 (0)2071048071; cornwallandplymouth.rec@hra.nhs.uk), ref: 20/SW/0156

Primary study design
Observational

Study design
Multi-centre feasibility cohort mixed methods study of three work packages

Study type(s)
Other

Health condition(s) or problem(s) studied
Monochorionic (MC) twin pregnancies with early-onset (prior to 24 weeks) selective fetal growth restriction (sFGR)

Interventions
A mixed-methods study has been designed to explore the current management of sFGR in MC twin pregnancy. This information will be used to inform a subsequent RCT comparing management options; intervention versus expectant management.

The study design involves 3 work packages, 1) a prospective UK multicentre study, 2) a qualitative study of women's and clinical staff's views and 3) an interactive consensus study and workshop, with each component informing the development of the next.

Work Package 1:
A prospective UK multicentre study to collect data on the management and clinical outcomes of MC twin pregnancies complicated by sFGR will be conducted. The study will determine the incidence, natural history and outcomes for sFGR in MC twin pregnancies according to whether they had expectant management or intervention. The study has been designed to provide vital up-to-date outcome data on untreated pregnancies with which to form a benchmark for comparisons of outcomes in a future RCT.

Participants with an MC twin pregnancy between 16+0-23+6 weeks gestation affected by sFGR will be recruited directly from the fetal medicine unit or antenatal clinic at nominated research sites. All women who meet the eligibility criteria for this study will be invited to participate by their attending clinician and/or midwife. Prior to taking part in the study, all women will have confirmation of their sFGR status completed based on an ultrasound scan performed within the preceding 72 hours. Once written informed consent has been provided participants will be registered in the study.

After study registration, there will be an 18-month data collection period (pregnancy management and outcome data). Other than providing permission for this data collection, participants will not have to take part in any other study-related activity. Participants will remain in the study for a maximum of 25 weeks (from 16+0 weeks' gestation [earliest point of eligibility] to 40+6 [recommended gestation of delivery for MC twins]) and during this period clinical care will be as per the local clinical team and the patient's wishes.

Work Package 2:
An embedded qualitative study will be used to understand parents' and clinical staff's views on the management of sFGR in MC twin pregnancy and the barriers to the use of interventions.

Parents will be recruited either as part of Work Package 1 or via a media advert. Clinical staff will be recruited from a database of sFGR experts or a media advert. Parents and clinical staff will be asked to contact the qualitative research team to register their interest in taking part. If eligible, participants will be given the option of a telephone, online or face-to-face (in line with the latest government guidance on COVID-19) interview. A member of the qualitative research team will contact participants to arrange an interview date and time. All interviews will last approximately 40 minutes and will be conducted by the qualitative research team using either the FERN parent or practitioner Interview Topic Guide.

Interviews will be conducted until the data saturation point, which is when major themes identified in the analysis of new data are reoccurring from previous participants/transcripts, and no new major themes are discovered. This is anticipated to be approximately 15-25 interviews per group.

To ensure sample variance the study will include parents with experience of intervention and expectant management of sFGR, bereaved and non-bereaved parents and clinical staff in favour of both fetal intervention and expectant management.

If divergence in opinions on trial intervention and acceptable outcomes is observed in the early analysis of interviews, a social media advert will be used to recruit parents and clinical staff to focus groups (North West of England) with the aim of reaching a consensus about an acceptable trial design. Parent and practitioner Focus Group Topic Guides will be developed based on interview findings.

Work Package 3: A survey will be conducted to identify current practices and opinions. This will enable the understanding of clinical uncertainties around management decisions. The results of the survey will then be used to inform a Delphi consensus process that will ultimately formulate an optimal trial design for use in a planned RCT in women with MC twin pregnancies complicated by sFGR. The consensus opinion on key preferred scenarios will then be used to develop a protocol for the planned trial.

A list of items/scenarios considered to be potentially important for an RCT will be formulated following the performance of an electronic survey of clinicians. This list of options will then be subjected to a Delphi process to reach a consensus on a preferred trial question and design.

The Delphi process will involve two rounds of electronic-based questionnaires, anonymised responses and feedback to reduce the list of clinical scenarios, prioritising those that are both uncertain and important. Stakeholder groups including PPIE co-applicants, parents, parent representatives, healthcare professionals and researchers will be invited to take part. Participation will be optional and informed consent will be assumed if a participant responds to the survey. The results of the Delphi process will then be fed into an interactive consensus meeting that will finalise a shortlist of key scenarios. Only stakeholders who complete both rounds of the Delphi study will be invited to participate in this meeting. The list of key scenarios will then be used to develop a draft protocol and plan the single most important trial.

Intervention Type
Mixed

Primary outcome(s)
The feasibility of conducting an RCT of active intervention versus expectant management in MC twin pregnancies with early-onset (prior to 24 weeks) sFGR will be measured using the following methods within the approved study timeline:

Work Package 1 - A collection of prospective data on the management and clinical outcomes of MC pregnancies complicated by sFGR (data collection from prospective eligible pregnancies from informed consent date to date of maternal discharge)

Work Package 2 - Perform a qualitative study involving interviews and focus groups with parents and clinicians to explore trial design, acceptability, feasibility and decision-making related to intervention or expectant management (qualitative interviews and focus groups)

Work Package 3 - Using information provided in work packages 1 and 2 to develop a consensus on a future definitive study (questionnaire and focus groups)

Key secondary outcome(s)
There are no secondary outcome measures

Completion date
30/11/2025

Eligibility

Key inclusion criteria
1. MC diamniotic twin pregnancy
2. Diagnosis of sFGR (EFW of one twin <10th centile + EFW discordance >25%)

3. Gestational age at diagnosis between 16+0 - 23+6 weeks based on ultrasound
4. Informed consent given by the participant and the consent form completed and signed

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Female

Total final enrolment
103

Key exclusion criteria
1. Singleton pregnancies
2. Maternal age under 18 years
3. TTTS
4. Twin anaemia polycythaemia sequence before enrolment
5. Other rare complicated MC twin pregnancies, such as twin reversed arterial perfusion syndrome
6. Known karyotype abnormality at enrolment
7. Known major fetal structural abnormality at enrolment, defined as a lethal, incurable or curable severe abnormality with a high risk of residual handicap
8. Indication for immediate delivery
9. Pre-term pre-labour rupture of membranes before enrolment
10. Women who lack the capacity to give informed consent
11. Any medical condition that compromises the woman’s ability to participate

Date of first enrolment
15/06/2022

Date of final enrolment
30/06/2025

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Study participating centre
Liverpool Women's NHS Foundation Trust
Liverpool Womens Hospital
Crown Street
Liverpool
United Kingdom
L8 7SS

Study participating centre
The Royal Jubilee Maternity Service
274 Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre
Burnley General Hospital
Casterton Avenue
Burnley
United Kingdom
BB10 2PQ

Study participating centre
St. George's Hospital (lanesborough Wing)
Blackshaw Road
Tooting
London
United Kingdom
SW17 0QT

Study participating centre
Manchester University Hospital NHS Ft (hq)
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Jessop Wing
Tree Root Walk
Sheffield
United Kingdom
S10 2SF

Study participating centre
St Michael's Hospital
Southwell Street
Bristol
United Kingdom
BS2 8EG

Study participating centre
Birmingham Women's Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2TG

Study participating centre
East Surrey Hospital
Canada Avenue
Redhill
United Kingdom
RH1 5RH

Study participating centre
Kingston Hospital
Galsworthy Road
Kingston upon Thames
United Kingdom
KT2 7QB

Study participating centre
Barts and the London NHS Trust
Alexandra House
The Royal London Hospital
Whitechapel

London
United Kingdom
E1 1BB

Study participating centre
University Hospital Coventry & Warwickshire
Clifford Bridge Road
Walsgrave
Coventry
United Kingdom
CV2 2DX

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Princess Anne Hospital
Coxford Road
Southampton
United Kingdom
SO16 5YA

Study participating centre
Birmingham Heartlands Hospital
Bordesley Green East
Bordesley Green
Birmingham
United Kingdom
B9 5SS

Study participating centre
Leeds General Infirmary
Great George Street

Leeds
United Kingdom
LS1 3EX

Study participating centre
London North West University Healthcare NHS Trust
Northwick Park Hospital
Watford Road
Harrow
United Kingdom
HA1 3UJ

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
The Royal Victoria Infirmary and Associated Hospitals NHS Trust
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Royal Surrey County Hospital
Egerton Road
Guildford
United Kingdom
GU2 7XX

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
United Kingdom
EH16 4SA

Study participating centre
University College London Hospitals NHS Foundation Trust
Elizabeth Garrett Anderson Wing, 25 Grafton Way
London
United Kingdom
WC1E 6DB

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
NIHR HTA

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

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 will be stored in a non-publicly available repository, University of Liverpool, Research IT, REDCap (FERN Study), https://redcap.liverpool.ac.uk.

The type of data stored is enrolment and eligibility, informed consent, maternal demographics, prospective pregnancy data including scan measurements, a record of any interventions required during the pregnancy and, the pregnancy outcomes. Access is only available to recruiting centres for inputting relevant prospective pregnancy data on behalf of their centre and, the FERN study management team. Note: centres can only access data relating to their specific centre. Consent from participants is required and obtained. The data is anonymised.

Results will be published after the study has completed WP1 recruitment and analysed the data. Results will be published on a study population basis, with no references to cases or particular case identifiers. Neither the study statistician nor the Chief Investigator will have access to any personal information relating to the study participants. As part of the qualitative work packages, brief quotations from interviews and/or focus groups may be included in publications/reports in an anonymised format; there will be no references to cases or particular case identifiers. In terms of confidentiality, data arising from this study will not include any personal identifiers and will only be accessed by nominated members of the core research teams, as per the ethical approval.

IPD sharing plan summary
Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/08/2024	09/09/2024	Yes	No
Other publications		09/08/2024	10/09/2024	Yes	No
Other publications		02/07/2024	10/09/2024	Yes	No
Other publications		20/02/2024	10/09/2024	Yes	No
Other publications		24/01/2025	16/04/2025	Yes	No
Participant information sheet	version 3.0	23/03/2023	15/08/2023	No	Yes
Participant information sheet	version 4.0	03/10/2023	08/11/2023	No	Yes
Participant information sheet	version 5.0	15/07/2024	17/07/2024	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes