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A clinical trial to find out the optimal oral iron dosing schedule for the prevention of anaemia in pregnant women (PANDA-Dose study)

Submission date
06/12/2022

Recruitment status
No longer recruiting

Registration date
27/04/2023

Overall study status
Completed

Last Edited
02/09/2024

Condition category
Pregnancy and Childbirth

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Around a third of UK pregnant women develop anaemia (reduced numbers of red blood cells) caused by a lack of iron. Anaemia may mean that women experience general health problems such as excessive tiredness. Severe anaemia during pregnancy might increase the risk of a baby being stillborn,
born early, or born small (with a low birth weight). It may also increase the risk of blood loss during childbirth and affect a baby's development. We know that treating anaemia after it develops does not reduce all the risks. This study describes the second project within a larger research programme, called 'Primary prevention of maternal ANaemia to avoid preterm Delivery and other Adverse outcomes (PANDA)'. The aim of PANDA is to find out whether anaemia can be prevented in the first place by giving iron tablets to improve the well-being of mothers and babies. In this study, the team aims to test three oral iron schedules (a once-daily dose, an alternate-daily dose and a three-times-a-week dose) in order to determine the best dose of oral-iron supplementation for preventing anaemia with minimal adverse effects. How many tablets are taken by a mother will be counted, and a validated questionnaire will be used to ask about adherence.
The study will see how different doses of oral iron affect changes in haemoglobin during pregnancy and will record the possible side effects that may be due to taking iron. The team will also record how many mothers completed the trial visits and data collection. A subset of participants will be given a behavioural intervention developed from the first project of the PANDA programme, to help women to adhere to oral iron supplementation. Overall, the findings from this study will tell us about the best dose of oral iron to be tested in a large national trial of oral iron supplementation.

Who can participate?
Healthy, non-anaemic pregnant women less than 14 weeks into their pregnancy

What does the study involve?
Study participants will be randomly allocated by a computer to one of the three groups. Each group instructs the participants to take their medication at different frequencies. They will need

to come to the hospital for antenatal visits around weeks 13 and 28 of their pregnancy and will need to provide extra blood samples at that time and also following delivery. Participants will be contacted by the research team by phone or email for follow-up between these visits.

What are the possible benefits and risks of participating?
Taking iron supplements may help participants by preventing iron-deficiency anaemia, which may provide health benefits for the participant and their baby. The information gained from this trial will help us find out the best dose to use in the next stage of the PANDA programme. Our goal is to improve the health and well-being of mothers and their babies by preventing anaemia during pregnancy. There can be side effects from taking iron supplements. Some side effects include abdominal pain, nausea and vomiting, constipation, diarrhoea, dark stools, lack of appetite and mouth ulcers.

Where is the study run from?
The study is run by NHS Blood and Transplant Clinical Trials Unit, with clinical and academic input from the University of Oxford, the University of Nottingham, the University of Wolverhampton and the University College London amongst others (UK)

When is the study starting and how long is it expected to run for?
September 2019 to August 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
PANDA study team, panda@nshbt.nhs.uk

Contact information

Type(s)
Scientific

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-003316-51

Integrated Research Application System (IRAS)
301769

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 50086, IRAS 301769

Study information

Scientific Title
A pilot clinical trial to test the acceptability and feasibility of different doses of oral iron supplementation to prevent maternal anaemia - PANDA-Dose Study

Acronym
PANDA-Dose Study

Study objectives
The study hypothesis is related to the PANDA research programme. To investigate the effects of providing prophylactic iron supplementation to pregnant women on anaemia and associated adverse maternal and infant outcomes.

The primary purpose of the dose study is to identify an optimal preventative dosage regimen of oral iron supplementation to take forward to be tested in the definitive trial (WS3) of the PANDA programme.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 13/09/2021, Wales Research Ethics Committee 5 (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2922 940910, (0)2922 940954, (0)2922 941106; Wales.REC5@wales.nhs.uk), ref: 21/WA/0247

Study design
Randomized open-label mixed interventional and behavioural study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Iron supplementation in pregnant women

Interventions
Overall design
This study is an open-labelled randomised trial. Participants will be randomised to one of its three dose arms, 200 mg ferrous sulfate daily (containing 65mg elemental iron), 200 mg ferrous sulfate on alternate days and 200 mg ferrous sulfate three times per week (e.g. Mon/Wed/Fri).

Participant identification and recruitment
Healthy non-anaemic pregnant women will be recruited initially from two sites (The Royal Wolverhampton NHS Trust and Oxford University Hospitals NHS Foundation Trust). A third site may be added if required. Information about the study will be provided to women at their first contact with the maternity services. This would
usually be given to them by their community midwives but could also be at their antenatal clinics, ultrasound dating and early pregnancy assessment units. We will also display information about the trial in antenatal clinics and early pregnancy assessment units and on public-facing research pages for each maternity unit, PPI groups, social media and trial website. Interested participants will be able to contact the local research team directly.

Potential participants may also be identified and approached by their care team (or local research team if different) such as through hospital clinic lists and other databases, and they will be contacted by phone and sent the trial information pack.

A screening log will be maintained which records information about the women approached including age, gestational week, parity, ethnicity, numbers declined and reason for the decline, ineligible and reason for ineligibility, consented and eligible.

Randomisation
After signing the informed consent form and completing eligibility checks at the baseline visit, participants will be randomised to one of the three-dose arms in a 1:1:1 ratio and will also be randomised 1:1 to whether they will receive a Medication Event Monitoring System (MEMS) cap. The MEMS cap automatically records the date and time of every occasion the bottle is opened and closed. Randomisation will be carried out using an electronic system.

Trial visits and assessments
Screening:

Routine blood tests and medical history that are performed at their initial routine booking visit (< week 13+6 days gestation) will be used to screen for eligibility. There will not be any extra trial screening visits. Further checks on eligibility, if not previously performed (physical assessment and medical history) will be done when the women attend clinic visits and will be carried out before consent as part of routine procedures. Those who are eligible and willing to take part will sign the informed consent form and carry on with the rest of the trial procedures.

Baseline visit 1 (part of a routine visit, usually at their antenatal visit or dating scan):
Participants will be asked questions about their medical history if not recorded at the booking visit (e.g. previous pregnancies, assessment of haemoglobinopathy screening and previous anaemia and treatment), and undergo a physical examination which includes weight and height measurements.

Participants will be asked about the concomitant medications in particular whether they are taking any iron-containing supplements. These supplements are allowed but the exact frequency and doses of elemental iron consumed will be recorded.

Blood samples will be collected for routine analysis of full blood count and ferritin, if not collected at booking. Research blood samples will be collected and stored for future detailed CRP and iron studies (analysis of hepcidin, Serum iron, Ferritin, Transferrin and Transferrin receptor (TfR)).

Participants will be randomised and prescribed the study oral iron supplements as per randomisation allocation. They will also be provided information about who to contact if they have any queries or concerns.

Participants will be assessed for baseline side effects symptoms.
(Study specific) Remote assessments A [Week 16 gestation (+/- two weeks) and B (Week 24 gestation (+/- two weeks)]:

Participants will be contacted by the local research team either by phone or email, or a face-to-face visit if they wish, for assessment of side effect symptoms.

Visit 2 (part of the routine visit at Week 28 gestation (+/- two weeks)):
Visit 2 is a study-specific face-to-face visit.
Participants will be asked about any changes to their concomitant medications and will be assessed for any side effects or symptoms.
Blood samples will be collected for routine analysis of full blood count and ferritin. Research blood samples will be collected and stored for future CRP and detailed iron studies. Participants are asked to return any remaining iron tablets in their original boxes/bottles and the tablets will be counted to check for compliance. Participants will also be asked about medication adherence through a short questionnaire (MARS-5 questionnaire).

Visit 3 (delivery and birth):
If delivery occurred at or before V3, data at V3 and V2 will be combined (blood samples will be collected once).
Blood samples will be collected for routine analysis of full blood count and ferritin. Research blood samples will be collected and stored for future CRP and detailed iron studies.

We will also record information about:
- the infant’s birth weight, gestation at birth, and whether or not neonatal care is needed.
- Maternal estimated blood loss at delivery

- Prescription of oral or intravenous iron at or prior to discharge
- Breastfeeding at discharge

Withdrawal
Participants may withdraw from the study intervention at any time without affecting their standard of care in any way. We will ask the participant for the reason for withdrawal, though the participant is not required to provide one. The study physician may also withdraw the participant from the study intervention based on medical judgement. Participants who are withdrawn from the intervention will remain in the study for the purpose of follow-up and data analysis unless they withdraw their consent from all stages of the study. Data collected up to the point of withdrawal will continue to be used for analysis. Any participant who is withdrawn from the intervention or study will not be replaced.

Intervention Type
Mixed

Primary outcome(s)
1. Adherence is measured using the following methods at 28 weeks:
1.1 Proportion of participants considered adherent to their dose schedule based on a count of returned tablets
1.2 Medication Adhesion Report Scale-5 (MARS-5) adherence questionnaire score
1.3 In those women that receive a Medication Event Monitoring System (MEMS) cap, the proportion of planned doses taken as scheduled according to the MEMS cap

2. Maternal haemoglobin concentration in pregnancy measured using blood tests between randomisation and 28 weeks

3. Types and frequency of symptoms reported by women which may be associated with iron supplementation at baseline remote visits assessments at Weeks 16 and 24 gestation (+/- two weeks), and at Week 28 gestation (+/- two weeks)

4. The following recruitment and protocol compliance variables measured using medical/study records and screening log at the end of the study
4.1 Proportion of approached women who consented.
4.2 Proportion of participants who completed the trial visits and data collection.
4.3 Use of iron-containing supplements

5. Fidelity, feasibility and acceptability of the behavioural intervention measured using the following methods throughout the study :
5.1 Audio recordings and completed checklists of delivered intervention components and website usage
5.2 Survey and interview data assessing pregnant women and healthcare professional views on feasibility and acceptability

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

Completion date
31/08/2023

Eligibility

Key inclusion criteria
1. Healthy non-anaemic pregnant women of all parities (haemoglobin concentration (Hb) > = 110 g/l) at booking or screening.
2. 13 weeks + 6 days gestation or less
3. Age 18 and above
4. Able to give informed consent and willing to fulfil trial requirements

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Total final enrolment
300

Key exclusion criteria
Women with the following conditions will be excluded:
1. Known haemoglobinopathies
2. Anaemia of any type, defined by BSH guidelines
3. Severe gastrointestinal disease, affecting tolerability of oral iron
4. Allergies to iron
5. Multiple pregnancies, given the higher iron demands
6. Known haemochromatosis
7. Recent red cell transfusion, within 1 month

Date of first enrolment
17/01/2022

Date of final enrolment
07/10/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
New Cross Hospital
Wolverhampton Road
Heath Town
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
New Cross Hospital
Wednesfield Road
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SR4 7TP

Study participating centre
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Study participating centre
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E1 1BB

Study participating centre
Whipps Cross University Hospital
Whipps Cross Road
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E11 1NR

Sponsor information

Organisation
NHS Blood and Transplant

ROR
https://ror.org/0227qpa16

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

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

Individual participant data that underlie all published PANDA-dose study trial results will be available upon request from NHSBT CTU, CTU@nhsbt.nhs.uk, after de-identification (text, tables, figures and appendices). Beginning 9 months and ending 5 years following article publication, data will be shared with investigators whose use of the data has been assessed and approved by an NHSBT review committee as a methodologically sound proposal. Data will be shared to achieve the aims in the approved proposal.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		29/08/2024	02/09/2024	Yes	No
Basic results		01/08/2024	01/08/2024	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes