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The use of iron administered as an infusion into a vein compared to the use of iron tablets taken by mouth for treating Nigerian women with iron deficiency anaemia during pregnancy

Submission date
08/12/2020

Recruitment status
No longer recruiting

Registration date
10/12/2020

Overall study status
Completed

Last Edited
24/03/2025

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
Iron deficiency anaemia is a condition where a lack of iron in the body leads to fewer red blood cells. Anaemia in pregnancy is a public health burden with a high incidence in Africa. Currently pregnant women who are anaemic are treated with high-dose iron tablets taken by mouth if it is mild or moderate in severity. Those who have severe anaemia are given blood. Some women do not tolerate the tablets well as they may develop side effects like constipation, stomach pain, nausea or vomiting. There are iron preparations in existence that can be given in infusion (drip) form and have been found to be safe, and their use for the treatment of iron deficiency anaemia in pregnancy is currently being evaluated. The aim of this study is to compare the effectiveness of ferric carboxymaltose given as an infusion through a vein versus oral ferrous sulphate taken by mouth for treating iron-deficiency anaemia in pregnancy, and to compare the acceptability, safety and the cost-effectiveness of these two forms of iron preparation in pregnant Nigerian women with moderate and severe iron deficiency anaemia at 20 – 32 weeks (5 - 7 months) of pregnancy.

Who can participate?
Pregnant women aged between 15 and 49 who are anaemic at the time they are registering for antenatal care in the hospital.

What does the study involve?
Information is collected about the participants' health and pregnancy and a blood sample is taken. Participants are randomly allocated to one of two drug treatments. The drug may be a preparation that will be added to an infusion (drip) for administration only once and over 30 minutes, or it may be in tablet form which will be taken by mouth three times a day until delivery. During pregnancy, their blood will be checked regularly and they will be asked questions at each visit and assessed for depression using a questionnaire on three occasions in the course of the study. Participants will be monitored all through pregnancy, through delivery and until 6 weeks after they have delivered. Their babies will also be examined after delivery to

get some information such as the birth weight and will also be followed up to collect information on their immunization status.

What are the possible benefits and risks of participating?
Though the drugs to be used in this study have been found to be relatively safe in pregnancy, it is still possible to suffer some side effects from any of the medications. Participants will be monitored closely to identify any side effect early and treat at no cost. All the trial drugs will be given free of charge and all the tests relating to this research will also be done for free. Participants will be given contacts of their caregivers and will be sent regular reminders about their appointments. The findings of this study will improve the knowledge about treatment of anaemia in pregnancy and enable existing treatments to be changed if need be in order to improve the well being of pregnant women and the outcome of their pregnancy.

Where is the study run from?
University of Lagos/Lagos University Teaching Hospital (LUTH) (Nigeria)

When is the study starting and how long is it expected to run for?
November 2020 to June 2023

Who is funding the study?
Bill and Melinda Gates Foundation (USA)

Who is the main contact?
Prof. Bosede B. Afolabi
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Study website
https://ivontrial.com

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2021-002867-23

IRAS number

ClinicalTrials.gov number
NCT04976179

Secondary identifying numbers
PACTR202012843695208

Study information

Scientific Title
Intravenous versus oral iron for iron deficiency anaemia in pregnant Nigerian women (IVON): an open label, randomized controlled trial

Acronym
IVON

Study objectives
Current hypothesis as of 27/06/2022:

Hypothesis 1: The researchers expect a lower prevalence of anaemia at 36 weeks' gestation, a reduction in incidence of preterm delivery, and improvement in other maternal and perinatal outcomes among the intravenous iron, compared with the oral iron group.
Hypothesis 2: The researchers expect intravenous ferric carboxymaltose to be more acceptable, feasible and cost-effective than oral ferrous sulphate in the treatment of moderate to severe IDA in pregnancy

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Previous hypothesis as of 15/12/2020:

Hypothesis 1: The researchers expect a lower prevalence of anaemia at 36 weeks' gestation, a higher increase in maternal haemoglobin concentration levels at 4 weeks post treatment initiation, and improvement in other maternal and perinatal outcomes among the intravenous iron, compared with the oral iron group
Hypothesis 2: The researchers expect intravenous ferric carboxymaltose to be more acceptable, feasible and cost-effective than oral ferrous sulphate in the treatment of moderate to severe IDA in pregnancy

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Previous hypothesis:

Hypothesis 1: The researchers expect a 14% lower prevalence of anaemia at 36 weeks' gestation and a 1g/dl increase in maternal haemoglobin concentration levels at 4 weeks post treatment initiation among the intervention group, compared with the control group.
Hypothesis 2: The researchers expect intravenous isomaltoside to be more cost-effective than oral ferrous sulphate in the treatment of moderate to severe IDA in pregnancy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 02/12/2020, Lagos University Teaching Hospital Health Research and Ethics Committee (P.M.B. 12003, Surulere, Lagos, Nigeria; +234 (0)15850737, +234 (0)15852187, +234 (0)15852209; luthethics@yahoo.com), ref: ADM/DCST/HREC/APP/3971
2. Approved 17/01/2021, National Health Research and Ethics Committee (chairman@nhrec.net, +234-09-523-8367), ref: NHREC/01/01/2007
3. Approved 23/04/2021, National Agency for Food Drug Administration and Control (NAFDAC) (der.headquarters@nafdac.gov.ng, +234-09-523-8367), ref: NAFDAC/DER/VCTD/IVON/VOL.2

Study design
Multicenter interventional parallel open-label individually randomized controlled trial with a cost-effectiveness analysis

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

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

Interventions
Current interventions as of 27/06/2022:

Eligible women will be admitted on a day case basis into the dedicated ward or day room for treatment initiation. They will be individually randomized in a 1:1 ratio to receive either intravenous ferric carboxymaltose or oral iron. "Sealed envelope" will generate the randomisation code list, shared ONLY with the unblinded pharmacist by email, who will then label each drug kit with a code according to the randomisation list and send to the appropriate study site. As each new patient is recruited in a particular site, her details will be entered into an electronic tablet and a code is generated that corresponds to the codes on a particular drug kit. She is then given a labelled drug kit that corresponds to her assigned code. The intervention group will receive intravenous ferric carboxymaltose will be 20 mg/kg body weight (but not exceeding 1000mg) given in 200 ml of normal saline as a single-dose infusion administered over 15 – 20minutes. The control group will receive oral ferrous sulphate 200 mg (65 mg elemental iron) three times daily from enrolment till delivery.

Previous interventions as of 12/04/2021:

Eligible women will be admitted on a day case basis into the dedicated ward or day room for treatment initiation. They will be individually randomized in a 1:1 ratio to receive either intravenous ferric carboxymaltose or oral iron. "Sealed envelope" will generate the randomisation code list, shared ONLY with the unblinded pharmacist by email, who will then label each drug kit with a code according to the randomisation list and send to the appropriate study site. As each new patient is recruited in a particular site, her details will be entered into an electronic tablet and a code is generated that corresponds to the codes on a particular drug kit. She is then given a labelled drug kit that corresponds to her assigned code. The intervention group will receive intravenous ferric carboxymaltose will be 20 mg/kg body weight (but not exceeding 1000mg) given in 250 ml of normal saline as a single-dose infusion administered over 15 minutes. The control group will receive oral ferrous sulphate 200 mg (65 mg elemental iron) three times daily from enrolment till delivery.

Previous interventions:

Eligible women will be admitted on a day case basis into the dedicated ward or day room for treatment initiation. They will be individually randomized in a 1:1 ratio to receive either

intravenous iron isomaltoside or oral iron. "Sealed envelope" will generate the randomisation code list, shared ONLY with the unblinded pharmacist by email, who will then label each drug kit with a code according to the randomisation list and send to the appropriate study site. As each new patient is recruited in a particular site, her details will be entered into an electronic tablet and a code is generated that corresponds to the codes on a particular drug kit. She is then given a labelled drug kit that corresponds to her assigned code. The intervention group will receive iron isomaltoside 20 mg/kg single dose, maximum 1500 mg diluted in 100 ml 0.9% Normal Saline infusion and given over 30 minutes. The control group will receive oral ferrous sulphate 200 mg (65 mg elemental iron) three times daily from enrolment till delivery.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Intravenous ferric carboxymaltose, oral ferrous sulphate

Primary outcome measure
Current primary outcome measure as of 14/03/2022:
1. Prevalence of maternal anaemia (diagnosed as haemoglobin less than 11g/dl), at 36 weeks' gestation, measured with a haematological auto-analyser.
2. Incidence of preterm birth, measured at delivery.

Previous primary outcome measure:
1. Prevalence of maternal anaemia (diagnosed as haemoglobin less than 11g/dl), at 36 weeks' gestation, measured with a haematological auto-analyser
2. Maternal haemoglobin levels measured using HemoCue at 4 weeks post-initiation of treatment and at delivery measured with a haematological auto-analyser

Secondary outcome measures
Current secondary outcome measures as of 20/07/2023:
1. Safety and tolerability, including the incidence of hypophosphatemia and severity of maternal adverse effects measured using medical records at Day 1 and 4 weeks post enrolment, at 36 weeks gestational age and at 6 weeks post delivery; added 12/04/2021: serum phosphate concentration measured with laboratory assays using maternal blood and cord blood taken at delivery
2. Severe maternal events, specifically, haemorrhage, sepsis, shock and the need for blood transfusion measured using medical records at delivery
3. The incidence of low infant birth weight (<2.5 kg), prematurity (<37 weeks’ gestation as dated from the last menstrual period or a first-trimester ultrasound scan), stillbirth and neonatal mortality (birth till 28 days of life), the proportion of infants being breastfed at 1, 2 and 4 weeks of life, and receiving BCG, oral polio and hepatitis vaccination in the same time period, measured using medical records
4. Depression linked to the emotional well-being of mothers measured using the validated Edinburgh Postnatal Depression Scale at enrolment, 36 weeks gestational age and 7 days post delivery
5. Maternal haemoglobin levels measured using HemoCue at 4 weeks post-initiation of

treatment and at delivery measured with a haematological auto-analyser
6. Prevalence of maternal iron deficiency (diagnosed by serum ferritin level less than 30 ng/ml) at 36 weeks' gestation measured using laboratory assay

Previous secondary outcome measures from 14/03/2022 to 20/07/2023:
1. Safety and tolerability, including the incidence of hypophosphatemia and severity of maternal adverse effects measured using medical records at Day 1 and 4 weeks post enrolment, at 36 weeks gestational age and at 6 weeks post delivery; added 12/04/2021: serum phosphate concentration measured with laboratory assays using maternal blood and cord blood taken at delivery
2. Severe maternal events, specifically, haemorrhage, sepsis, shock and the need for blood transfusion measured using medical records at delivery
3. The incidence of low infant birth weight (<2.5 kg), prematurity (<37 weeks' gestation as dated from the last menstrual period or a first-trimester ultrasound scan), stillbirth and neonatal mortality (birth till 28 days of life), the proportion of infants being breastfed at 1, 2 and 4 weeks of life, and receiving BCG, oral polio and hepatitis vaccination in the same time period, measured using medical records
4. Depression linked to the emotional well-being of mothers measured using the validated Edinburgh Postnatal Depression Scale at enrolment, 36 weeks gestational age and 7 days post delivery
5. Maternal haemoglobin levels measured using HemoCue at 4 weeks post-initiation of treatment and at delivery measured with a haematological auto-analyser

Previous secondary outcome measures:
1. Safety and tolerability, including the incidence of hypophosphatemia and severity of maternal adverse effects measured using medical records at Day 1 and 4 weeks post enrolment, at 36 weeks gestational age and at 6 weeks post delivery; added 12/04/2021: serum phosphate concentration measured with laboratory assays using maternal blood and cord blood taken at delivery
2. Severe maternal events, specifically, haemorrhage, sepsis, shock and the need for blood transfusion measured using medical records at delivery
3. The incidence of low infant birth weight (<2.5 kg), prematurity (<37 weeks' gestation as dated from the last menstrual period or a first-trimester ultrasound scan), stillbirth and neonatal mortality (birth till 28 days of life), the proportion of infants being breastfed at 1, 2 and 4 weeks of life, and receiving BCG, oral polio and hepatitis vaccination in the same time period, measured using medical records
4. Depression linked to the emotional well-being of mothers measured using the validated Edinburgh Postnatal Depression Scale at enrolment, 36 weeks gestational age and 7 days post delivery

Overall study start date
01/11/2020

Completion date
15/06/2023

Eligibility

Key inclusion criteria
1. Pregnant women aged 15 to 49 years old between 20- and 32-weeks' gestational age
2. Baseline (enrolment) laboratory-confirmed moderate or severe anemia (Hb <10 g/dl)

Participant type(s)
Patient

Age group
Mixed

Lower age limit
15 Years

Upper age limit
49 Years

Sex
Female

Target number of participants
1,056

Total final enrolment
1056

Key exclusion criteria
Current exclusion criteria as of 27/06/2022:

1. Medically confirmed significant bleeding, major surgery or received blood transfusion within the last 3 months.
2. Severe symptomatic anemia needing urgent correction with blood transfusion.
3. Anemia of other cause besides IDA e.g., Sickle cell anemia.
4. Clinically confirmed malabsorption syndrome.
5. Hypersensitivity to any form of iron treatment.
6. History of any immune related illness e.g., SLE, Rheumatoid arthritis.
7. Preexisting maternal depression or other psychiatric illness.
8. Severe allergic reactions such as severe asthma.
9. History of severe drug allergy.

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Previous exclusion criteria:

1. Medically confirmed significant bleeding, major surgery or received a blood transfusion within the last 3 months
2. Symptomatic anaemia with dyspnea or fatigue and a need for urgent correction
3. Concurrent anaemia of another cause besides IDA
4. Clinically-confirmed malabsorption syndrome or hypersensitivity to any form of iron treatment
5. Preexisting maternal depression or other psychiatric illness

Date of first enrolment
09/08/2021

Date of final enrolment

15/12/2022

Locations

Countries of recruitment
Nigeria

Study participating centre
Lagos University Teaching Hospital
Idi-Araba
Lagos
Nigeria
100254

Study participating centre
Lagos Island Maternity Hospital
Campbell Street
Lagos Island
Lagos
Nigeria
101231

Study participating centre
Mother and Child Centre
1st Avenue
1st Gate
Festac Town
Amuwo-Odofin
Lagos
Nigeria
102312

Study participating centre
Simpson Primary Health Centre
Simpson Street
Ebute-Metta
Lagos
Nigeria
101212

Study participating centre

Iwaya Primary Health Centre
Omotola street
Iwaya
Lagos
Nigeria
100213

Study participating centre
Aminu Kano Teaching Hospital
Zaria Road
Kano
Nigeria
7002333

Study participating centre
Sheikh Jeddah General Hospital
Bello Road 700224 Sabon Gari West
Kano
Nigeria
700271

Study participating centre
Bammali General Hospital
Emir Palace Road 700224 Kan Karofi
Kano
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713261

Study participating centre
Kumbotsu Comprehensive Primary Health Centre
Kumbotsu
Kano
Nigeria
700104

Study participating centre
Sharada Primary Health Centre
Sharada
Kano
Nigeria
700234

Study participating centre
Kabuga Comprehensive Primary Health Centre
Gwarzo Rd, Kofar Dukayuwa
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Kano
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Sponsor information

Organisation
University of Lagos

Sponsor details
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Sponsor type
University/education

Website
http://www.unilag.edu.ng/

ROR
https://ror.org/05rk03822

Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

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

Location
United States of America

Results and Publications

Publication and dissemination plan
The researchers plan to publish the protocol in a peer-reviewed journal. The researchers plan to publish the study findings in high-impact peer-reviewed journals. The findings of the study will be presented at conferences (both international and local) so as to disseminate the findings to a large body of professionals in the field of Obstetrics and Gynaecology. The findings will be used in developing standard operating care manual/ protocol for the management of iron deficiency anaemia in pregnancy. The researchers will issue press releases about the findings of the study.

Intention to publish date
30/06/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository. The researchers will store the data and deposit it in 'Open Science Framework' after approval is obtained from the ethics committee. The researchers will also provide metadata along with the data to describe it. No patient identifier will be included in the data shared. Potential new users may access our data including the metadata on the 'Open Science Framework'. The researchers will share the data at the time of publication of our first paper. The assigned DOI number, the OSF website details and the approach to data sharing will be included as an appendix to all publications emanating from this research to facilitate accessibility to our data and metadata. The researchers will also share these at any conference presentation both international and local, and also on the study website to facilitate access by other researchers.
The individual participant data (IPD) sharing will commence at the time of the first publication or within 6 months of completing the study. The duration of IPD sharing will be 2 years. The tentative start date for IPD sharing is 01/01/2024 and the tentative end date is 31/12/2025.
Key access criteria include:
1. The principal investigator will bear overall responsibility for this data and will be responsible for deciding whether to supply research data to a potential new user. The CMUL HREC will provide an independent oversight function.
2. Data will be made available at the time of publication, at the latest. Depending on the nature of the data itself, data may be made available earlier, either on an individual basis to interested researchers and/or potential new collaborators.
3. The researchers will ensure that the informed consent forms clearly spell out and seek consent for future data sharing. However, only de-identified data will be shared.
4. All external users will sign and be bound by our data sharing agreements and will not be

allowed to use the data for reasons other than stated in their application.
5. IPD sharing will be by open access on Open Science Framework during the period of IPD sharing.

IPD sharing plan summary

Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			11/12/2020	No	Yes
Protocol article		08/09/2022	09/09/2022	Yes	No
Other publications	Qualitative study	13/02/2024	13/02/2024	Yes	No
Funder report results		03/09/2023	30/09/2024	No	No
Statistical Analysis Plan		30/09/2024	30/09/2024	No	No
Dataset		24/03/2025	24/03/2025	No	No
Other files	CSR data dictionary	24/03/2025	24/03/2025	No	No