Comparison of Oral Ferrous Sulfate to Intravenous Ferumoxytol in Antepartum Iron Deficiency Anemia

Informed Consent Form

NCT04253626

November 28, 2023

Are you participating in any other research studies? _____ Yes _____No

SUMMARY

Your consent to participate is being sought for research purposes and your participation is entirely voluntary. The purpose of the research is to determine the extent to which the treatment of antepartum iron deficiency anemia in the third trimester with intravenous iron increases hemoglobin by birth compared to oral iron supplementation. The duration of your participation is expected to be around 12 weeks long. The study procedures will include randomizing you to either receive oral iron medications or intravenous iron infusions. There is a 50% chance for you to be assigned to either treatment arm. You will be expected to complete a follow-up blood draw 4 weeks and 8 weeks after initiation of whichever study treatment you are randomized to to re-check your iron levels. You will also be asked to complete four short surveys during your participation. Both treatments are standard treatments used for medical care and FDA approved but there are always unforeseeable risks when participating in any research study that will be discussed in greater detail further along in this consent form. Potential benefits of participation include improved hemoglobin levels at the time of delivery, less risk for blood transfusion, and less risk of adverse maternal and neonatal outcomes often associated with anemia in pregnancy. The alternative to participating in this study would be to continue planned medical care during your pregnancy.

PURPOSE OF RESEARCH

You are invited to participate in a research study of iron deficiency anemia treatments during pregnancy. We hope to determine the extent to which the treatment of antepartum iron deficiency anemia in the third trimester with intravenous iron increases hemoglobin by birth compared to oral iron supplementation. Intravenous iron (ferumoxytol) and oral iron (ferrous sulfate) are both FDA-approved and will be used according to labeling. You were selected as a possible participant in this study because you are pregnant and have been diagnosed with iron-deficiency anemia.

Anemia in pregnancy is a risk factor for increased rates of maternal and perinatal morbidity, and iron deficiency represents over 70% of the anemias diagnosed in pregnancy. Iron deficiency anemia (IDA) presents one treatable and potentially reversible cause of severe maternal morbidity. However, guidelines do not exist for treatment of IDA in late pregnancy and the current standard– oral iron supplementation – is known to have adverse side effects and a slow rate of effect.

The study aims to add key research in this area to improve the management of antepartum anemia, particularly for women that are at risk for poor outcomes with later presentations of anemia in pregnancy.

If you decide to terminate your participation in this study, you should notify Dr. Deirdre Lyell at 650-725-5720.

This research study is looking for 80 participants with iron deficiency anemia in pregnancy, and the study will be done in Stanford University.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 2 years, with 12- 16 weeks of active participation by each participant. Medical record review will be done for you and your baby.

PROCEDURES

If you choose to participate, the Protocol Director Dr. Deirdre Lyell and her research study staff will randomize you to either receive oral iron medications or intravenous iron infusions. There is a 50% chance for you to be assigned to either treatment arm.

A blood draw (about 2 teaspoons) for iron studies may be performed prior to initiation of any intervention to confirm eligibility if not already performed as part of standard clinical care. A complete metabolic panel and/or complete blood count may also be performed.

If you are randomized to the intravenous iron infusion arm, you will:

- You will receive an intravenous injection of ferumoxytol 510 mg to be started between 28-35 weeks gestation. The iron infusions take about 15-30 minutes and you will be monitored for another 15-30 minutes post-infusion to observe for any adverse reactions. Your vital signs will also be closely monitored during and post-infusion.

- If your hemoglobin level is between 7-8.9 g/dL, you will be given 2 doses of the iron infusions 3-8 days apart
- If your hemoglobin level is between 9- 10.9 g/dL, you will be given a single dose of the iron infusion
- Prior to each infusion of IV iron, you will receive a 650mg dose of oral tylenol (acetaminophen) approximately 20 minutes before beginning the infusion
- Have a blood draw of about 1 teaspoon each at 4 and 8 weeks after completion of the iron infusion/s to check for your complete blood counts

If you are randomized to the oral iron medication arm, you will:

- Start taking iron (ferrous sulfate) tablets by mouth every other day after randomization up to the day of delivery
- If your hemoglobin level is between 7-8.9 g/dL, you will need to take 2 tablets of iron 325 mg tablets every other day until you deliver
- If your hemoglobin level is between 9- 10.9 g/dL, you will need to take 1 tablet of iron 325 mg tablet every other day until you deliver
- Have a blood draw of about 1 teaspoon each at 4 weeks and 8 weeks after you start taking the oral iron medication to check for your complete blood count (CBC)

You will be asked to complete four short surveys total about your symptoms: one at the time of enrollment and at 1, 4, and 8-12 weeks after initiating therapy. The survey is 21 questions in length and should take no more than 5 minutes to complete.

Your and your baby's medical records will be reviewed.

This research will not include whole genome sequencing.

Your blood samples collected for the study will not be saved for future research. Your information and/or specimens will not be used or distributed for future research studies even if all identifying information is removed.

Any of your specimens which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of specimens do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Future Use of Private Information and/or Specimens:

Research using private information and/or specimens is an important way to try to understand human disease. You are being given this information because the investigators want to save private information and/or specimens for future research.

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Take the study drug as instructed.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Keep the study drug in a safe place, away from children and for your use only.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Deirdre Lyell at 650-725-5720.

If you withdraw from the study, or the study medication is stopped for any reason:

- Your iron deficiency anemia may persist

The Protocol Director may also withdraw you from the study and the study medication may be stopped, without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

- Venipuncture will be performed multiple times during the study and risks of venipuncture include mild discomfort for a short period of time, bruising, and in rare cases infection.
- Oral ferrous sulfate is commonly used during pregnancy and postpartum for treatment of iron deficiency anemia. Adverse reactions of oral ferrous sulfate include gastrointestinal effects such as darkening of stools, abdominal pain, heartburn, nausea (7.5%), vomiting (5.0%), and constipation.
- Ferumoxytol is an FDA approved formulation of intravenous iron for treatment of iron deficiency. Intravenous iron is routinely used to treat pregnant women with severe iron deficiency anemia. The following adverse reactions of ferumoxytol iron have been reported: nausea (3.1%), dizziness (2.6%), hypotension (2.5%), peripheral edema, headache, vomiting, abdominal pain, chest pain, itching, fever, back pain/muscle spasms and rash, including permanent skin discoloration due to IV extravasation.
- Serious hypersensitivity reactions, including anaphylaxis, which can be life threatening and fatal have been reported to occur in Ferumoxytol. Anaphylaxis has been reported to occur for approximately 34 persons per 100,000. Symptoms associated with an allergic reaction such as wheezing, shortness of breath have been reported in 3.7% of the cases. For this reason, we exclude patients with a history of two or more medication allergies. In addition, we infuse the medication slowly over 30 minutes,

and you will be monitored for at least 30 minutes afterwards. Ferumoxytol can also transiently affect the diagnostic capability of MRI for 3 months after infusion.

- If you are randomized to the intravenous iron infusion arm, you will need to come in for a separate appointment/s to do the infusion/s and will need to allot some time for the procedure
- It is possible that this study may involve unforeseeable risks to the participant or her fetus, including death.
- Adverse reactions of oral acetaminophen include gastrointestinal symptoms, loss of appetite, itching, rash, headache, dark urine, clay-colored stools, or jaundice, and rarely, serious allergic reactions.

POTENTIAL BENEFITS

Potential benefits include improved hemoglobin levels at the time of delivery, less risk for blood transfusion, and less risk of adverse maternal and neonatal outcomes often associated with anemia in pregnancy.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

There are no alternative treatment approaches or procedures other than to choose not to participate in the study. If you choose not to participate, your clinical provider will determine with you the appropriate treatment as based on clinical guidelines.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your baby's health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your and your baby's health information will be used or disclosed in the study. Your and your baby's information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The study would like to determine the extent to which the treatment of antepartum iron deficiency anemia in the third trimester with intravenous iron increases hemoglobin by birth compared to oral iron supplementation.

You and your baby's health information will be used to contextualize the results we get from the study samples and the assigned study intervention. The health information we collect for use in a publication for this study will be coded.

Your information relating to this study, including your name, medical record number, and date of birth may be shared with the billing offices so that claims may be appropriately submitted to the study sponsor or to your insurance company for clinical services and procedures provided to you during the course of this study.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to:

Dr. Deirdre Lyell
453 Quarry Road
Palo Alto, CA, 94304

What Personal Information Will Be Obtained, Used or Disclosed?

Your and your baby's health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, you and your child's name, medical record numbers, phone numbers, address, electronic mail address, and dates of birth. We will also collect obstetrical and neonatal outcome data, including dates of service. We will collect you and your child's clinical data including demographics, medical history, maternal prenatal/ obstetric history, ultrasound imaging/radiology data, laboratory test results, diagnosis codes, prescriptions or medications, pregnancy complications, labor and delivery data, clinical narratives, maternal post-partum outcomes, treatment regimens, neonatal data including outcomes and complications.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Dr. Deirdre Lyell
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary

- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- Other collaborators as approved by the IRB
- Maternal and Child Health Research Institute
- The Food and Drug Administration
- The National Institutes for Health

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on December 31, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment/Reimbursement

You will not be paid to participate in this research study.

Costs

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor

The National Institutes for Health is providing financial support and/or material for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Deirdre Lyell at 650-725-5720. You should also contact her at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact Maternal Fetal Medicine Research at 650-725-5720.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and

IRB Use Only
Approval Date: November 28, 2023
Expiration Date: November 23, 2024

- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

The IRB determined that the permission of one parent is sufficient for research in accordance with 21 CFR 50.55.

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of Witness Date

_____
Print Name of Witness

(e.g., staff, translator/interpreter, family member)

- *Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.*
- *The English consent form (referred to as the "Summary Form" in the regulations):*
  - *Must be signed by the witness AND the Person Obtaining Consent (POC).*
  - *The non-English speaking participant/LAR does not sign the English consent.*
  - *The non-English speaking participant/LAR should not sign the HIPAA participant line*
  - *If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.*