A Pilot Trial for the Prevention of Anemia in Pregnancy at Time of Birth Admission: A Randomized Clinical Trial

National Clinical Trial (NCT) Identified Number: NCT04253626

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Prevention of Anemia in Pregnancy at Time of Birth Admission: A Randomized Clinical Trial

Objective: Our goal is to provide evidence on the most effective treatment of persistent iron deficiency anemia (IDA) late in pregnancy among all women. Our aims are to evaluate the 1) mean change in hemoglobin in IV iron group vs oral iron over 4 weeks, and 2) the mean change in hemoglobin in the IV vs oral iron group pre-delivery

Organization: Stanford University Maternal-Fetal Medicine Division

Clinical Center: Stanford/LPCH OB clinic

Design Type: Open Label Randomized clinical trial

Inclusion Criteria:

1. Pregnant patients 18 years old and above receiving prenatal care at Stanford/LPCH OB clinic
    a. Hemoglobin < 11 g/dL, serum ferritin < 30 ug/dL and or transferrin saturation (TSAT) < 20%
    b. Between 24-34 weeks' pregnancy
    c. (study will offer iron studies to determine eligibility for patients eligible by hemoglobin if labs not ordered by primary obstetrician/health care provider per standard of care)
2. Singleton pregnancy
3. Viable Pregnancy
4. Hemodynamically stable

Exclusion Criteria:

1. Patients unable to give informed consent
2. Known allergy/hypersensitivity to IV iron
3. Inflammatory Bowel Disease or history of gastric bypass surgery
4. Dialysis-dependent Chronic Kidney Disease
5. Known Hemoglobinopathies such as sickle cell disease, beta- thalassemia, alpha thalassemia (not including trait)
6. Folate/Vitamin B12 deficiency
7. Known malignancy
8. History of multiple medication allergies (> 2 allergies)
9. Hemoglobin above 12 or less than 7 g/dL
10. Patients with complex past medical histories which may include history of multiple medication allergies, connective tissue disorder, etc.
11. Medication allergy to Tylenol
12. Placenta previa

Interventions:

1. Active group: IV iron (ferumoxtyol)
2. Standard group: Oral Ferrous sulfate

Medications:

Ferrous sulfate 325mg tablets every other day or 650mg (two 325mg tablets) po every other day per protocol

Ferumoxytol intravenous iron – 510mg x1 dose or 510mg x2 doses per protocol

Tylenol 650mg tablets (or 325mg tables x 2)
Analysis: Intent to Treat
Outcome Measures:
Primary composite:

- Correction of anemia by time of birth
  - Change in hemoglobin
- Rates of blood transfusion postpartum

Primary safety outcome:

- Rates of adverse events
- Compliance with medication
- Severe neonatal composite morbidity
- Severe maternal morbidity

Timetable:
Recruitment: 0-9 months
Data Collection: 0-12 months
Complete follow up: 0-16 months
Final data/primary analysis: 12-16 months

Sample size: 80

1. INTRODUCTION

This manual gives detailed instructions on procedures for the Prevention of Anemia in Pregnancy (PAP) Trial. It is meant to serve as a reference guide for study staff, including investigators, coordinators, study nurses, and data managers.

1.1 Organizational Structure

This study is governed by Stanford Maternal Fetal Medicine Division, Labor and Delivery, and the Clinical Translational and Research Unit site.

1.1.1 Steering Committee (SC)

A Maternal-Fetal Medicine Clinical Review Unit (CRU) and Data Safety Monitoring Board (DSMB) that brings together the multi-disciplinary will oversee implementation including: finalizing the clinical protocol, training and certification, monitoring recruitment, data coordination and quality control, DSMB recommendations and IRB-related issues. The SC will also make final decisions about data analysis and interpretation, secondary analyses, presentation at scientific meetings and publications.

1.1.2 Responsibilities

The responsibilities of these individuals are described briefly here:

PI and co-PIs are responsible for ensuring the proper conduct of the study clinic site including recruitment as specified in the protocol and accurate collection of the data.
Other specific duties include:

a. Obtaining and maintaining IRB approval and training for study personnel
b. Obtaining sufficient study areas for study personnel to interview patients and perform study procedures, including storage of study medication and other study supplies.
c. Participate in study- related meetings or conference calls
d. Familiarity and training for REDCap based data entry system by appropriate staff.
e. Screen potential participants for eligibility and consent them. It is important to ensure the patient's primary obstetric provider agrees to follow the study treatment protocol during pregnancy.
f. Randomize per protocol to intervention arms – both arms to receive medication
g. Follow participants during the antepartum, delivery and 6 (4-12) weeks postpartum periods: with labs as indicated in the protocol and with pre- and post-intervention surveys to monitor patient symptoms and adverse effects

h. Facilitate collection of labs at 24-28 weeks gestation (preferred window, but may collect up to 34 complete weeks), labs at 4 and 8 weeks post-initiation of pill for standard group and post-treatment of intravenous iron in the active group and delivery.
i. Trained research staff will conduct research data abstraction from patient medical records, and conduct participant interviews, pill counts, and other direct participant contact as required by the protocol. Research staff at CTRU, will undergo training to ascertain response to severe adverse outcomes, specifically identification of hypersensitivity reactions to intravenous iron.
j. Investigators will participate in blinded review of outcomes in order to confirm the primary and other key outcomes.
k. Maternal outcomes will be ascertained through 6 weeks including a postpartum visit in this window. If unscheduled visits occurred at another facility, obtain medical records release (if one has not already been obtained) to order hospital visit records.
l. All newborn outcomes will also be ascertained through 6 (4-12) weeks through medical records chart review. If unscheduled visits occurred at another facility, obtain medical records release (if one has not already been obtained) to order hospital visit records.
m. Data collection forms for maternal outcomes, newborn outcomes, NICU outcomes, and postpartum clinic/hospital outcomes will be completed by study personnel. These forms will be used to enter the clinical data into the study data base.

The Study Coordinator will be responsible for the day-to-day operations of the study at the clinical center, including recruitment and data collection processes. This responsibility includes the following:

a. Establishing a method of training and monitoring to ensure primary obstetric providers are following the study treatment protocol during the pregnancy.
b. Establishing a method to ensure that all potential participants receive medications and appropriate follow up
c. Establishing a method that for screening women with IDA who are potentially eligible for the study e.g. dedicated clinic days or sessions.
d. Assures that study drug is available at all times by checking the available drug supply at least weekly. The current workflow is that Stanford's pharmacy will dispense medications with Stanford's CTRU.
e. Meeting with Stanford Investigational Drug Pharmacist pharmacy and/or site CTRU if necessary, to understand center specific drug request procedures.
f. Arranging for the ordering and storage of study supplies.
g. Collecting maternal and neonatal information necessary to complete all study forms.
h. Will abstract information related to primary and other key outcomes, and assure that the PI and IRB (if required by institution) is notified of any primary outcome events and adverse events.
i. Training additional staff as needed in data collection, forms completion and data entry.
j. Coordinating data entry, including controlling access to the REDCap and study unit as applicable, and assuring that required back-up security and confidentiality procedures are maintained.
k. Organizing and maintaining records, including the protocol, data forms, reports and correspondence

1.2 Procedures for Participant Confidentiality

The REDCAP database will contain PHI linked to the patient's clinical data. The MFM Research team members are the only one who will be able to access this database. A study/screening number will be used to identify each participant. Site will maintain a log of participant names and medical record numbers.

1.3 Training and Site Initiation

A training session for study coordinators will be held before recruitment starts. The purpose of the training workshop is to review the study design, objectives, procedures, data collection forms and a demonstration of the REDCap data base. The coordinators, in turn, are responsible for training any additional staff assigned to this study. Clinical site initiation to enroll and randomize participants is dependent upon completion of a series of preliminary tasks. These include completion of appropriate regulatory approvals (IRBs).

Site staff training, certification, and receipt of all study supplies including medications will need to be completed as well as the development of a site recruitment plan. Fulfillment of the following are requirements before start of study:

1. Review of the final version of the study protocol, data forms and manual, and study medications.
2. IRB approval and consent forms on file at Stanford. Due to COVID, also consider e-consent process.
3. Completion of training and data entry of forms.
4. Training with Stanford's CTRU

1.4 IRB approval

Approval by an IRB before any participant examination or data collection can begin. Once a study has been approved, any additional information about the study that relates to participant safety (i.e., protocol changes, significant adverse events, changes in the consent form) also needs to be submitted to the IRB.

1.5 Interim IRB Review/Approval

After initial approval, an IRB must be notified any time about:

- Recruitment Brochures and Advertisements
- Form Letters or Study information sent to participants
- Protocol Amendments
- Protocol Deviations
- Serious Adverse Events (SAEs)
- Unanticipated problems
- Consent Form Revisions

1.5.1 Protocol Amendments

All protocol changes must be sent to an IRB as protocol amendments.

1.5.2 Regulatory Binder

The Study Regulatory Binder is the administrative binder that serves as the regulatory record of each clinic's participation in the IDA study. It should be kept current and available for review by the DSMB or in the event of an audit. The binder should include current copies of:

- Protocol and revisions
- All protocol amendments
- IRB submissions and approvals, IRB renewals and any submitted protocol deviations and log, IRB correspondence (adverse events reports)
- Copies of IRB approved informed consent document(s)
- Research participant advertisements, (e.g. patient brochures, pamphlets) patient education materials, newsletters, etc.
- Current correspondences relating to human subjects research (may keep separate correspondence file)
- Enrolled patient log with pertinent identifier information (randomization number if needed)
- List of study drug formulary and package inserts

Other items that may also be included are: recruitment plans, a set of study forms, CVs or biosketches for study staff, staff responsibility logs, essential elements of informed consent checklist, protocol deviation logs or other requirements from Stanford institution

2. STUDY INFORMATION

2.1 Study Rationale

Iron deficiency is the most common cause of anemia in pregnancy in the United States (Mei). Our study will add key evidence to improve the management of antepartum IDA in late pregnancy, when women are at particularly high risk for poor outcomes. Our study will also assess previously unstudied outcomes, notably blood transfusion.

Rationale for change in intravenous iron

The initial proposal aimed to conduct a prospective open label randomized clinical trial comparing standard of care (SOC) oral ferrous sulfate to IV FCM for the treatment of anemia in pregnancy. FCM was the IV iron formulation of choice based on a FER-ASAP clinical trial and meta-analysis supporting safety of iv irons in pregnancy [1–4]. It also has required less time per infusion (30min) and max course of 2 doses. As highlighted by the reviewers, hypophosphatemia is an increasing concern noted in studies of nonpregnant populations[5]. Further review of previously

existing study protocols shows that serum phosphate was not assessed in initial trials evaluating safety in pregnant women. Huang et al is the only study that reports the rate of hypophosphatemia in a cohort of 20 pregnant women, one of which developed clinically relevant hypophosphatemia. The expertise of Stanford faculty Dr. Chertow, a co-author in "Randomized Clinical trial of IV iron induced hypophosphatemia", graciously provided further assistance and helped to contextualize previous research experience with CKD patients[5]. As a precaution, this study proposal has been significantly modified to exclude the use of FCM.

2.2 Background

Anemia in pregnancy is a risk factor for increased rates of maternal and perinatal morbidity [6]. Antepartum anemia has been linked to higher rates of blood transfusion, preterm delivery, low Apgar scores, NICU admissions, and delay in neuro-cognitive motor development[6,7]. Iron deficiency represents over 70% of the anemias diagnosed in pregnancy. Other causes of anemia can include malnutrition, folate or vitamin B-12 deficiency, hemoglobinopathies, chronic infections and poor access to prenatal care[8,9]. This effect is further amplified in non-Hispanic Black, Mexican American pregnant women, and women with a history of greater than two prior births[10]. Black pregnant women often experience the highest rates of antepartum anemia, approximately two-to-threefold compared to other racial/ethnic groups [11].

Physiologically, iron utilization increases from approximately 2 mg/day in the non-pregnant state to 5-6 mg/day in pregnancy [12]. Furthermore, blood volume expansion by approximately 50% and the increase of plasma cell volume by 35% contribute to heightened consumption of iron stores with advancing gestation of pregnancy[13]. Current guidelines support supplementation with 27 mg of elemental iron in pregnancy, an equivalency commonly found in over the counter prenatal vitamins [9,14]. Oral ferric salts (such as ferrous sulfate) are recommended for IDA in fractionated dosing of 100-200 mg of elemental iron/day[15]. Additional prescriptions for iron are influenced by laboratory assessments at the initiation of prenatal care and 24-28 weeks of pregnancy[7]. Oral preparations, although cheaper, are associated with adverse gastrointestinal side effects, noncompliance, and limited interval increase in hemoglobin at the time of delivery compared to intravenous preparations [16]. A meta-analysis concluded greater than 70% of pregnant women experienced an adverse side effect, largely GI, with oral iron treatment and discontinuation of oral medication in approximately half of patients prescribed [17].

Consequently, some women will require parenteral administration of iron. Newer preparations of intravenous iron solutions have been well-tolerated with low anaphylaxis type reactions and fewer adverse side effects than older formulations [3,4]. Intravenous iron sucrose in pregnancy has been shown to be efficacious in addressing anemia in late pregnancy [3,18], yet drawbacks include dosing (max 200mg/dose), frequency (avg 4-5 infusions) and duration (1-2hrs each). The contemporary class of IV irons available in the U.S. include ferric carboxymaltose (FCM), ferumoxytol and low molecular weight dextran (LMWD). LMWD has the advantage of being administered in a single dose; yet requires a test dose is recommended prior to infusion and concerns regarding rates of anaphylaxis limited widespread use[19]. An investigation demonstrated that most of the severe adverse events were associated with its predecessor high molecular weight iron[19]. Ferumoxytol is a "superparamagnetic iron oxide" that creates an iron-carbohydrate complex with elemental iron that allows for more rapid infusion[20]. Ferumoxytol is FDA approved for adults with IDA[20]. Animal studies of ferumoxytol have not shown teratogenic effects at human doses; however, teratogenicity was seen in animal studies at levels six times that of human dosing[20,21].

As a precaution, IV irons are not recommended in the first trimester to decrease the possibility of harm during organogenesis. The FDA updated labelling for pregnancy and lactation considerations list consideration for IV iron use in second/third trimester of pregnancy and "it is not known if ferumoxytol changes breast milk concentrations." A clinical trial with ferumoxytol in pregnancy is near completion with standard dosing (510mgx2 or single dose infusion)(clinical trials.gov) for all patients[22]. By comparison, our proposed trial recommends hemoglobin based dosing extrapolated from the Ganzoni formula[23]. Ferumoxytol safety data for anaphylaxis is less than < 1%[19,24].

Our study will add key evidence to support the management of antepartum IDA in late pregnancy, when women are at particularly high risk for poor outcomes. In collaboration with the CMQCC (Medical Director Dr. Elliott Main, Co-I on this proposal), our study will also assess feasibility for a large scale, multicenter quality intervention for California hospitals.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Benefits

Potential benefits of treatment with iron during pregnancy including repletion of iron stores and decreased incidence of SMM. This potential benefit may be increased in diverse racial/ethnic populations that experience higher rates of iron deficiency anemia. A 2013 meta-analysis suggested daily oral iron use could increase birth weight of infant, concerns in a follow-up study were raised about risk associated with over supplementation.

Over supplementation is less likely to be a risk in this cohort as we correcting only iron deficiency anemia and not iron deficiency, it's precursor.

Iron crosses the placenta and is also thought to be beneficial for breastfed infants. A recent review did not reveal studies that suggest adverse effect of iron in breast milk.

2.3.2 Assessment of potential risks

Oral Iron Risks

Pregnancies in experimental animals: Large-dose dietary iron supplements were not teratogenic when tested in mice and rats. However, pregnant rabbits fed maternally toxic dose levels of an iron supplement had offspring with an increased incidence of defects of the central nervous system and skeleton. Retrospective studies have raised concern of teratogenic effect of oral iron in the first trimester, however, the findings were not replicated in larger studies. Observational studies have not found an increase in congenital defects with oral iron use.

Oral ferrous sulfate adverse effects include darkening of stools < 80%), abdominal pain (~70%), heartburn, nausea (68%), flatulence (38%), and diarrhea (23%).

Note: Intentional severe iron intoxication is potentially fatal and has been associated with adverse fetal and maternal outcomes such as preterm birth, miscarriage. There have been reports of patient overdose of oral iron with use of desferoxamine if severe.

Patients in this study will receive oral medication at interval lengths.

Intravenous Ferumoxytol Risks

IV iron is indicated in pregnant women who cannot tolerate oral iron, those with persistent anemia despite oral iron treatment and in pregnant women with impaired absorption [7]. Ferumoxytol, is part of a newer class of IV irons that can be administered more quickly and have less adverse reactions due to a tighter binding of elemental iron by carbohydrate shells [25,26]. As of 2018, Ferumoxytol is FDA approved for adults with IDA. Animal studies of ferumoxytol have not shown teratogenic effects at human doses; teratogenicity was seen in animal studies at levels 4x that of human dosing[20]. IV iron transfusions are not administered in the first trimester due to concerns of this time period being the most critical for organogenesis. There are ongoing clinical trials with ferumoxytol in pregnancy near completion with standard dosing for all patients. Comparison studies of FCM to ferumoxytol have shown that ferumoxytol has a lower anaphylaxis rate and <1% hypophosphatemia[27].

Information adapted from package insert

Black Box warning on label: "Serious hypersensitivity reactions, (some fatal), including anaphylaxis may occur, presenting with cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, or unresponsiveness even in patients who previously tolerated ferumoxytol. Infuse over ≥15 minutes and have equipment for resuscitation and trained personnel experienced in handling emergencies immediately available during use. Monitor patients for signs/symptoms of hypersensitivity reactions, including blood pressure and pulse during and ≥30 minutes (until clinically stable) following administration. Other hypersensitivity reactions have also occurred (pruritus, rash, urticaria, wheezing). Patients with multiple drug allergies may have greater risk of anaphylaxis; elderly patients with multiple or serious comorbidities who develop hypersensitivity and/or hypotension after ferumoxytol may be at greater risk for serious adverse events."
Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving ferumoxytol in less than 1%. Initial symptoms may include hypotension, syncope. Unresponsiveness, cardiac/cardiorespiratory arrest.

Hypersensitivity reactions have occurred in patients in whom a previous ferumoxytol dose was tolerated. Other adverse reactions potentially associated with hypersensitivity have occurred (pruritus, rash, urticarial reaction and wheezing). Patients with a history of multiple drug allergies may have a greater risk of anaphylaxis with parenteral iron products.

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis.

Administration of ferumoxytol may transiently affect the diagnostic ability of magnetic resonance imaging. Alteration of MR imaging studies may persist for up to 3 months following the last ferumoxytol dose. The most common serious AEs reported in ferumoxytol-treated

patients were syncope, gastroenteritis, seizure, pneumonia, hemorrhagic anemia, and acute kidney injury.

A separate protocol is referenced below for the management of hypersensitivity reactions.

IV ferumoxytol in pregnancy

Ferumoxytol is a "superparamagnetic iron oxide" that creates an iron-carbohydrate complex with elemental iron that allows for more rapid infusion[20]. Ferumoxytol is FDA approved for adults with IDA[20].

- Animal Studies

Animal studies of ferumoxytol have not shown teratogenic effects at human doses; however, teratogenicity was seen in animal studies at levels six times that of human dosing[20,21]. As a precaution, IV irons are not recommended in the first trimester to decrease the possibility of harm during organogenesis.

- FDA label for pregnancy

The FDA updated labelling for pregnancy and lactation considerations list consideration for IV iron use in second/third trimester of pregnancy and "it is not known if ferumoxytol changes breast milk concentrations."

- Studies in Pregnancy

A clinical trial with ferumoxytol in pregnancy is near completion with standard dosing (510mgx2 or single dose infusion)(clinical trials.gov) for all patients[22]

Safety measures for this study include the following:

- Obtain VITALS prior to transfusion (see table below) for reference range in pregnancy
- Monitor patients for signs and symptoms of hypersensitivity during and after IV iron administration for at least 30 minutes and until clinically stable following completion of the infusion. IV iron will only to be administered in sites where personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.
- Pregnant women in this study may receive up to a maximum dose of 1020mg ferumoxytol only; this is the max dose per course as outlined by the package label instructions. Each dose will be given as 510 mg IV infusion and if needed, a second dose of 510 mg ferumoxytol may be given 3-8 days after first infusion.
- Monitor patients for signs and symptoms of hypertension following each ferumoxytol administration.

Cardiac, Respiratory and Hematologic Physiologic Changes in Pregnancy

	Direction of Change	Percentage of Change or Normal Range in Pregnancy
Blood volume	↑	30%-40% increase
Heart rate	↑	Increases by 10-20 bpm
Cardiac output	↑	30%-60% increase
Systemic vascular resistance	↓	25%-30% decrease
Blood pressure	↓	10-15 mm Hg decrease in first two trimesters
Colloid oncotic pressure	↓	10%-15% decrease
Total lung capacity	↓	4%-5% decrease
Functional residual capacity	↓	20% decrease
Diffusion capacity	↔	No change
Tidal volume	↑	Increased
Respiratory rate	↔	No change
Minute ventilation	↑	50% increase
PaO_2	↑	Average 100-105
$PcaCo_2$	↓	Average 28-32
pH	↑	Mild respiratory alkalosis
A-a gradient	↑	Increase in late gestation to approximately 20
Protein S	↓	
Activated protein C resistance, fibrinogen, factor V, VIII, IX, X	↑	
Plasminogen activator inhibitor type 1 and 2	↑	
Activity of tissue plasminogen	↓	

Modified from Miller MA, Bourjeily G. Management of the critically ill pregnant patient. Pulmonary and Critical Care Update (PCCU). April 2009, 23 (Lesson 8); with permission.

Source: Williams Obstetrics and Gynecology, 25th Edition

Vital signs which suggest hemodynamic instability

- HR > 120
- Systolic Blood Pressure > 160 or Diastolic Blood Pressure > 110
    - (pts with controlled hypertension can be enrolled in the study)
- RR > 24 or less than < 10

*See Separate Section for management of adverse reactions

<u>Oral Acetaminophen Risks</u>

Acetaminophen is generally considered to be safe to use during pregnancy and has been categorized as Class B for all trimesters. Acetaminophen is known to cross the placenta during pregnancy, and acetaminophen administered during labor has been found in the umbilical cord blood at delivery (Levy 1975). There is no known association with teratogenicity, however few clinical studies have assessed safety (Collins 1981). More recent studies with poor power have suggested a link between prenatal acetaminophen use and asthma, lower intelligence quotient,

shorter male anogenital distance (predicting poor male reproductive potential), attention-deficit/hyperactivity disorder, poorer attention and executive function, and behavioral problems in childhood (Toda 2017). The Society of Maternal Fetal Medicine deems these studies as inconclusive as the methodologies were subject to recall bias and no data on dosing or frequency of use was incorporated into the analyses (Society of Maternal Fetal Medicine 2017). Thus, the current recommendation is to use acetaminophen for at the lowest dose for the minimal duration possible. We will be administering a single 650mg dose of acetaminophen in the course of this study, which is considered to be safe in pregnancy.

Adverse effects of oral acetaminophen include nausea, vomiting, abdominal pain, loss of appetite, itching, rash, headache, dark urine, clay-colored stools, or jaundice. Serious allergic reactions to acetaminophen can include rash, itching/swelling (including of the face/tongue/throat), severe dizziness, or difficulty breathing.

2.3.3 Risk Benefit/Ratio

Iron deficiency anemia at admission for birth hospitalization has been associated with increased severe maternal morbidity, preterm birth, low birth weight, incidence of C-section and more. Assessment of outcomes in this study will determine how treatment can improve maternal and neonatal outcomes.

3. OBJECTIVES

3.1 Primary Outcome

Perform a pilot randomized control trial of oral ferrous sulfate to IV ferumoxytol in women with IDA in the second and third trimester of pregnancy. We will *test the hypotheses* that 1) intravenous (IV) iron therapy will increase hemoglobin more with IV iron than oral iron over a 4 week period, approximately 0.8 g/dL in the IV group and 0.5g/dL in the oral arm[16,28] and 2) IV iron will improve anemia at the time of birth admission, 1.5 g/dL for IV iron and 1 g/dL for oral iron supplementation, the standard of care[28,29]

3.2 Secondary Outcome

Evaluate the

- rate of patients who discontinued treatment,
- the rate of adverse events associated with treatment,
- the need for blood transfusion postpartum
- symptoms of patients before, during, and at the completion of therapy

4. STUDY DESIGN

4.1 Overall Design

This will be an open-label randomized clinical trial at an academic tertiary care center comparing oral ferrous sulfate to intravenous (IV) ferumoxytol in pregnant women with IDA in the second or third trimester.

4.2 Justification for Dose

Historically, oral ferrous sulfate has been increased up to 2-3 tablets daily for anemia. However, this practice as come into question as women often have difficulty with completing oral treatment due to gastrointestinal side effects. Immediate release oral iron products are preferred for treatment of iron deficiency anemia; enteric coated and slow/sustained release preparations are not desired due to poor absorption (Hershko 2014; Liu 2012).

Further, there is increasingly more and more evidence optimal oral iron absorption occurs with single dosing every other day (Stoffel, et al 2020). There is also evidence to demonstrate intermittent dosing is also associated with less adverse side effects (RR 0.41, 95% CI 0.21 to 0.82; 6 studies, 1166 participants; moderate-quality evidence) (Cochrane 2019).

The dosing for intravenous iron was initially based on the Ganzoni formula. However, it was noted to be cumbersome as it was not practical to dose outside of the confines of elemental iron in the viable. Thus in clinical practice patients have received the standard dosing 510 mg x 2 and recently there was an investigation by Auerbach et al which demonstrated the efficacy of single dosing of 1020 mg in a single infusion (MA).

In regards to a pregnancy specific population, it is of particular interest if receipt of intravenous doing can be stratified by hemoglobin level ranges. There is retrospective data that suggests that intravenous iron dosing with respect to pre-pregnancy body mass index may also be an area of future concern.

4.3 End of Study Definition

The study will be complete once enrollment has been completed. The goal is 80 patients with 40 in each arm.

4.4 Sample Size

We estimated minimum sample size required for 90% power, one-sided α=0.025, and estimated effect sizes for the outcomes of change in proportion of women (Hg <11g/dL) by birth hospitalization based on the findings of previous studies[16,30]. Based on these parameters and allowing for 20% drop-out rate, the study requires 32 subjects per arm. The analysis plan and sample size calculation were developed in consultation with Maternal-Fetal Medicine Senior

Biostatistician, Stephanie Leonard, PhD (Co-I). We plan to recruit 80 patients to account for potential loss to follow up.

4.5 Timeline

Aim 1 Milestones	Q1	Q2	Q3	Q4
Extramural funding application preparation and submission. Letter of intent submitted to PCORI February 4th; full applications due May 5th.	X			
Patient screening and enrollment. Patients identified via CBC testing during the second trimester	X			
Randomization. Patients randomized to IV iron cohort or Oral iron cohort	X			
Intervention. IV iron cohort receives intravenous iron. Oral iron cohort prescribed ferrous sulfate tablets.		X	X	
Data Analysis and Manuscript Preparation and Submission.			X	X

5. STUDY POPULATION

5.1. Screening and Inclusion/Exclusion Criteria

General Screening guidelines

I. We will recruit Stanford Children's Health prenatal patients via screening by second trimester complete blood count results, which are routinely performed to screen for anemia performed at 24-28 weeks' gestation or may be performed for any other clinical indication, and with plans for delivery at LPCH. Patients can be included in the study up until 34 weeks.
   a. Patients will be eligible for the study if they meet the following criteria for IDA: hemoglobin 7-10.9 g/dL and serum ferritin <30 μg/L) (WHO).
   b. Patients on prenatal supplements with iron and/or taking oral iron in the early part of pregnancy but meeting other inclusion criteria will also be included in the study cohort.

II. Patients will be screened by chart review
   a. Patients will need to complete iron studies to appropriately determine eligibility
   b. Data obtained from the screening process includes a review of CBC screening at performed in the second trimester.
   c. Review will also include pregnancy dating information using the initial ultrasound, and other medical history information taken at the first prenatal visits. Other baseline information, including such items as contact information, vitals, demographic and pregnancy history information, concomitant medications, and lifestyle information will be reviewed to assess suitability for study participation.

d. Gestational age must be validated prior to enrollment using the latest ACOG criteria that compares LMP derived gestational age with ultrasound parameters. The ACOG criteria for gestational age determination are listed in section is as follows:

Gestational age assessment by ultrasonography in the first part of the second trimester (between 14 0/7 weeks and 21 6/7 weeks of **gestation**, inclusive) is based on a composite of **fetal** biometric measurements and has an accuracy of ± 7–10 days.

5.2 Inclusion Criteria

Women with a singleton, viable pregnancy greater than 24 weeks gestation based on the best clinical estimate according to ACOG criteria (see below) and have hemoglobin from 7-10.9 g/dL and serum ferritin < 30 ug.

In agreement with ACOG, we recommend that all pregnant women be screened for anemia at the initiation of prenatal care and second/third trimester with a CBC. As this study is focused on intervention in the >24 weeks gestation, we will not be proposing a treatment regimen with IDA identified prior to this time.

Ferritin is also an acute phase reactant and can be elevated in chronic illnesses. Therefore, the study would also include of women with a hemoglobin 7-10.9 g.dL and transferrin saturation < 20%.

5.3 Exclusion Criteria

If the basic screening criteria are met (patient has IDA by parameters outlined above), the next step is to review the exclusion criteria. Those without exclusions should be approached for study participation.

Assess the following exclusions:

1. History of hypersensitivity to intravenous iron. Out of an abundance of caution, pregnant women with this history will be excluded due to concern for increased risk of anaphylaxis
2. Known hemoglobinopathies. This was added as an exclusion criteria to remove the potential confounder that women with hemoglobinopathies such as sickle cell disease, thalassemia, may have a different physiologic response to intravenous iron.
3. History of Inflammatory Bowel Disease or history of gastric bypass surgery. Intravenous iron is the first line for treatment of iron deficiency anemia in individuals with inflammatory bowel disease due to concerns for impaired absorption of oral iron.
4. History of Dialysis-Dependent Chronic Kidney Disease (CKD). This category was added as patients with dialysis-dependent chronic kidney disease, because while the initial studies treated CKD patients with Ferumoxytol, these patients would require a complex dose adjustment due to decreased clearance.
5. Multifetal pregnancy (twins reduced to singleton or with vanishing twin syndrome prior to 14 weeks qualify)
6. Gestational age < 24 weeks (needs ultrasound confirmation)

7. High-risk co-morbidities for which treatment may be indicated: if patient with multiple medical problems important to discuss with primary obstetrician prior to enrollment.
8. Pt with history of with two or more medication allergies: patient with history of medical allergies can slightly increase the risk of hypersensitivity reactions.
9. Severe asthma or eczema
10. Pt with the following will need additional review of medical history prior to inclusion:
    a. Receiving treatment with beta blockers
    b. Systemic inflammatory disease (rheumatoid arthritis, lupus) or connective tissue disorder
    c. Severe anxiety
11. Medication allergy to Tylenol
12. Placenta previa

Women who meet inclusion criteria and do not have exclusion criteria may be approached for the informed consent process.

5.4 Screening/Re-screening

Patients may be included in the study up to 34 weeks 6/7 days. If the above inclusion criteria are met and exclusion criteria are absent, patients should be approached for study participation (if not already done) and randomization. All women who have a diagnosis of IDA should have the screening form initiated. The screening number will be generated electronically with REDCap is accessed and participant information is entered.

5.5 Gestational Age Determination

Gestational age will be determined by the most recent ACOG criteria with ultrasound required prior to randomization. If no ultrasound examination has been performed previously, one will be performed before the patient is randomized. **Only pregnant women with gestational age ≥ 24 0/7 weeks will be included.**

5.6 Informed Consent Process

An informed consent must be obtained before entry into the randomized trial. Full disclosure of the nature and potential risks of participating in the trial including the risks of being in the standard care group will be made. All potential participants will undergo the informed consent process as approved by the Institutional Review Board at each participating center. Any woman who is potentially eligible will be told about the study and asked if she is willing to participate. The point in the screening process at which a signed informed consent is required will be prior randomization. The study personnel conducting the informed consent process should emphasize the following study criteria during the informed consent process:

- Patients eligible based on hemoglobin will be offered iron studies if it's not already collected as part of routine prenatal care.

- Randomization to a treatment arm with iron to increase hemoglobin, with 50% chance to be assigned to either arm:
    - One group will receive oral iron
    - One group will receive intravenous iron
- Participants to sign medical release
- American College of Obstetrics and Gynecology recommends oral iron as standard of care and IV iron only for a select few medical indications
- Labs will be drawn 4 and 8 weeks post-initiation (Oral iron)/ post treatment (IV iron) and to evaluate anemia
    - Update: We will no longer perform study draw at 6 weeks postpartum, however, we will document labs performed as part of routine study care postpartum.
- Follow up to occur at clinic appointments or phone/email to evaluate symptoms associated with either treatment

Due to elevated rate of anemia in the Hispanic/Latinx/Latina population we will also have consents available in Spanish, or translators will be available for the consent process. A short form consent may also be used depending on the participant's preferred language.

All women who are considered for participation in the study (consent, decline or ineligible) should have a data entry form and entered into the electronic data system even if not randomized. Women who do not meet IDA criteria at 24-28 weeks screening visit, may be re-screened until such time that they meet exclusion criteria or they reach 34weeks' gestation.

5.7 Requesting Medical Release Forms

In order to obtain medical records from participants, each participant should sign a "Release of Medical Information" form. A signed Release of Medical Information form should be obtained at the time of, and preferably before, randomization. Clinical Site staff will be able to answer any questions about the procedure at the very beginning of their participation in the study. Also, reluctance to supply medical records may serve as a potential "red flag" that a potential participant may be an adherence or retention risk.

If a participant refuses to sign a Medical Release Form, probe for reasons for the refusal. Explain the importance of the records for the study and why they are needed. Some participants may be willing to sign a release that is specific to information needed for a particular outcome. If the participant continues to refuse, note the refusal in the participant's chart and continue to follow them according to the protocol if they consent to contacts and/or visits.

5.8 Background and Rationale for Hemoglobin, Serum Ferritin and Transferrin Saturation Cutoffs

In women without comorbidities, a serum ferritin <30 ng/mL can confirm the diagnosis of iron deficiency; levels ≥30 ng/mL rule out the possibility of IDA. Borderline levels of serum ferritin may be in the range of 30 to 40 ng/mL with chronic illnesses such as diabetes because ferritin is an acute phase reactant.

We will also test for iron studies including ferritin, serum iron, total iron binding capacity (TIBC), and calculation of transferrin saturation (TSAT) if not already collected by primary OB prior to inclusion in study.

TSAT below 20 percent can also demonstrate evidence of iron deficiency whether the ferritin level is low or normal. Iron supplements can falsely elevate the TSAT. To avoid this test interference, iron parameters should be drawn after an overnight fast, or the woman should simply be advised to avoid iron-containing foods or supplements to mitigate otherwise falsely elevated TSAT values.

5.9 Frequency of Labs

The timing of follow up labs is determined by the expected amount of time a participant should see an increase in hemoglobin. The hypothesis is that 1) intravenous (IV) iron therapy will increase hemoglobin more with IV iron than oral iron over a 4 week period, approximately 0.8 g/dL in the IV group and 0.5g/dL in the oral arm[16,28] and 2) IV iron will improve anemia at the time of birth admission, 1.5 g/dL for IV iron and 1 g/dL for oral iron supplementation, the standard of care[28,29]The estimates are informed from a 2018 study which reflected a 1.5 g/dL increase in hemoglobin by time of delivery in the intravenous group.[28]

The follow up and reassessment is further informed by Micheal Auerbach's et al approach to treatment of IDA in pregnancy.

6. RANDOMIZATION AND BASELINE VISIT PROCEDURES

In participants with IDA prior to 24 weeks' gestation, they can still be included in the study if they meet the inclusion criteria at 24 weeks gestation/ enrollment time frame. If IDA is a new diagnosis at the time of 24-28 weeks gestation, patients meeting the inclusion criteria be included.

In both groups, prenatal data will be obtained at the randomization visit. The randomization visit should occur with timing of lab results availability and prenatal visit if applicable.

Randomization may occur upon confirmation that all exclusion/inclusion criteria are satisfied and after verification of participant consent and HIPAA authorization. Of particular importance, careful consideration will be given the patient's prior history and medications to determine final eligibility and the appropriate study algorithm to follow (see below). Study staff will also verify participant contact information and obtain a Release of Information.

The MFM Research team will review the following before randomization:

- Complete review of all exclusion and inclusion criteria
- Informed consent obtained
- Iron studies and baseline labs to confirm eligibility
- Pre-intervention survey to assess symptoms

After randomization:

- Provide medication and instructions based on the treatment arm randomized to
- Provide the group algorithm to both patient and provider.

Once the participant is randomized, the treatment algorithms will be conspicuously placed in the patient's medical record (whether electronic or paper medical record is utilized) such that providers will be aware of treatment plan at all times.

In both groups, serial CBC follow up and survey for symptoms will be assessed. Baseline data consisting gestational age of pregnancy, body mass index, pre-pregnancy weight and other prenatal data including baseline BP at the randomization visit will be included.
Patients will be assigned to treatment groups by a concealed randomization allocation sequence using REDCap.

The categories of patients randomized:

Patients consenting to the study will be randomized 1:1 to two treatment groups

Group 1: Patients randomized to the IV iron group will receive treatment as follows:

- Women with Hgb 9-10.9 g/dL will receive one dose of 510 mg IV ferumoxytol
- Women with Hg 7-8.9 d/dL will receive two doses of ferumoxytol 510 mg 3-8 days apart for a maximum of dose of 1020 mg (see **Figure 2**).
- Patients will receive 650mg of Tylenol prior to initiation of the infusion
- The ferumoxytol is administered as an infusion for approximately 15-30 minutes. Patients will receive the IV iron at Stanford's Clinical and Translational Research Unit (CTRU) outpatient clinics with vitals collected before infusion and monitoring for 30minutes after infusion. Alternatively, patients who are admitted to the antepartum unit may receive the infusion inpatient.
  For the IV iron group, follow up labs will be performed at 4 and 8 weeks after completion of infusion/s;

Group 2: The standard of care oral iron group will be prescribed 1-2 ferrous sulfate 325 mg tablets to be taken by mouth **every other day** until delivery. Dosage will be as follows for standardization:

- one ferrous sulfate tablet every other day if Hg 9-10.9 g/dL, and
- two tablets once every other day if Hg 7-8.9 g/dL.
- Oral medications will be dispensed by the CTRU or by the Outpatient Investigational Pharmacy (final confirmation pending contracts)
- Follow up labs will be drawn for both groups. For the oral iron group, it will be drawn 4- and 8-weeks post initiation of treatment

Patients in both groups will complete post-intervention surveys at 1 week, 4 weeks, and 8-12 weeks after initiating therapy to monitor symptoms and adverse events.

6.1 Informed Consent

No study activities will be conducted until an IRB approval is obtained. Potential participants who may be eligible will be approached by the research staff. The research staff will only introduce the study with the patients after a member of the clinical care team acquires permission from the potential participant that they can be approached for a study. If interested, the research staff will discuss the study and obtain an informed consent from the participant.

Sufficient time will be given to participants to read the consent form, and to ask questions to ensure understanding.

An IRB-approved study brochure may be given to potential participants to provide more information about the study and the procedures involved.

6.2 Randomization visit: Study Groups

There will be 2 intervention groups, active treatment or standard care, based on randomization.

Group 1 (active treatment):

The starting dose and escalation of therapy in the active treatment arm are as follows:

Ferumoxytol: The patient will receive infusions at the Stanford's CTRU or in the Antepartum Unit

Ferumoxytol will be administered to participants with iron deficiency anemia with inclusion criteria as outlined above. Each single use vial contains 510 mg elemental iron / 15 mL.

Prior to infusion of ferumoxytol, patients will receive 650mg of Tylenol.

Participants with Hemoglobin between 9-10.9 g/dL will receive one dose of ferumoxytol (510mg). Participants with Hemoglobin between 7-8.9 g/dL will receive two doses (total 1020mg) of ferumoxytol with 3-8 days interval between doses per manufacturer instructions. The IV iron is administered as an infusion for approximately 15 – 30 minutes. Patients will receive the IV iron at Stanford's Clinical and Translational Research Unit (CTRU) outpatient clinics under the administration under trained Advanced Practitioner Provider/Research Clinic Nurse coordinator or in the inpatient Antepartum Unit. When administered via infusion, administer diluted as a slow IV infusion over at least 15 minutes. Patient should be in a reclined or semi-reclined position during the infusion; monitor for signs of hypersensitivity (including blood pressure and pulse) for at least 30 minutes after infusion. In the case hypersensitivity or side effects to medication, patients will be treated according to standard clinical guidelines, which may include administering Benadryl, Zofran, steroids, albuterol nebulizer, and in the cases of serious hypersensitivity, intramuscular epinephrine.

Note: Serious hypersensitivity reactions have been observed with rapid IV injection (<1 minute) (Macdougall 2014; Vadhan-Raj 2014). Wait ≥30 minutes between administration of ferumoxytol and other agents that may cause serious hypersensitivity reactions and/or hypotension (e.g., chemotherapy, monoclonal antibodies).

Group 2 (standard of care):
Ferrous sulfate: the patient will receive a bottle dispensed with 100 pills at a time.

Oral ferrous sulfate will be administered to participants identified with iron deficiency anemia as described above. One tablet every other day in patients with hemoglobin 9-10.9 g/dL and two tablets every other day will be provided for patients with hemoglobin levels between 7- 8.9 g/dL.

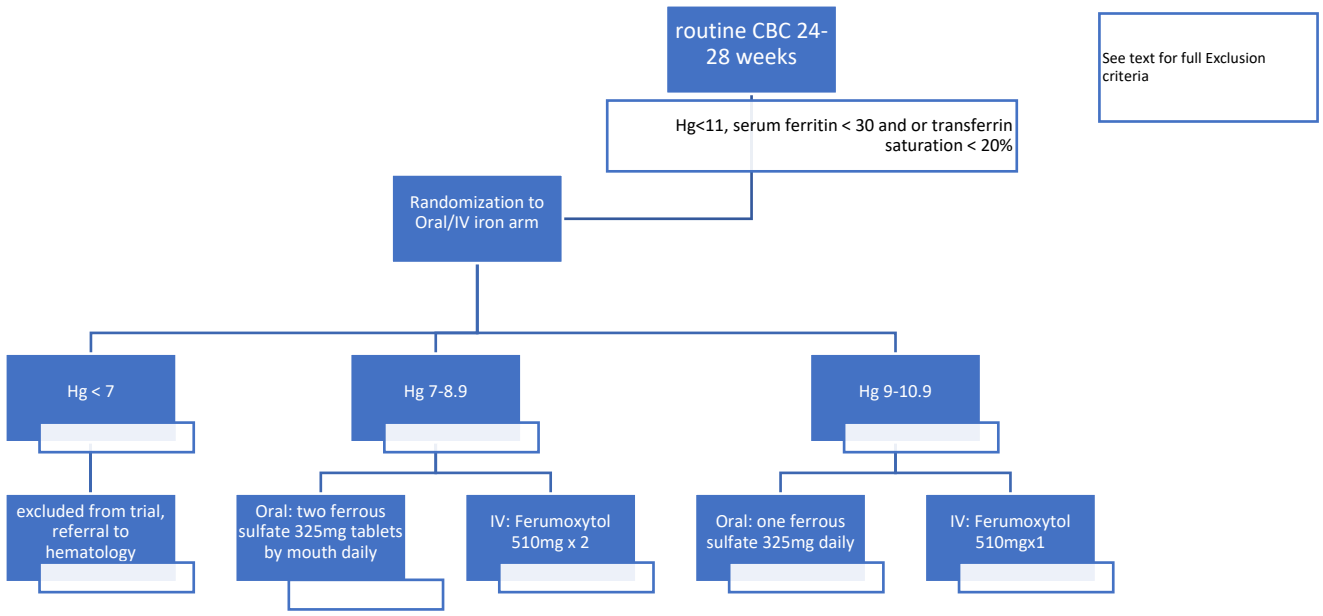
Tablet: 325 mg [elemental iron 65 mg].

6.3. Starting dose of Medications

Historically, suggested dosing of oral ferrous sulfate has been increased in frequency up to 2-3 times per day for treatment of anemia. However, this practice has come into question as women often have difficulty with completing oral treatment due to gastrointestinal side effects. Immediate release oral iron products are preferred for treatment of iron deficiency anemia; enteric coated and slow/sustained release preparations are not desired due to poor absorption (Hershko 2014; Liu 2012). Moreover, hepcidin has been found to be elevated immediately after taking oral iron, transiently decreasing absorption (Moretti 2015). A recent open-label, randomized controlled trials showed higher amounts of iron absorption with dosing every other day compared two daily dosing, with subsequent studies showing similar findings (Stoffel et. al., 2017). Thus, oral iron with be dosed every other day in this study.

The dosing for intravenous iron was initially based on the Ganzoni formula. However, it was noted to be cumbersome as it was not practical to dose outside of the confines of elemental iron in the viable. Thus, in clinical practice patients have received the standard dosing 510mgx2 and recently there was an investigation by Auerbach et al which demonstrated the efficacy of single dosing of 1020mg in a single infusion (MA).

Algorithm A: Randomization


routine CBC 24-28 weeks
See text for full Exclusion criteria
Hg<11, serum ferritin < 30 and or transferrin saturation < 20%
Randomization to Oral/IV iron arm
Hg < 7
Hg 7-8.9
Hg 9-10.9
excluded from trial, referral to hematology
Oral: two ferrous sulfate 325mg tablets by mouth daily
IV: Ferumoxytol 510mg x 2
Oral: one ferrous sulfate 325mg daily
IV: Ferumoxytol 510mgx1

7. POST RANDOMIZATION VISITS AND MANAGEMENT OF IDA

7.1 Post Randomization Visits and management of IDA for both groups at 4 weeks

Group 1: (IV iron) Follow up visits
Important for patient to maintain prenatal care, beyond 28 weeks gestation: frequency of visits determined by primary OB, this is often every 1-2 weeks

- 4 weeks post treatment labs to be timed with prenatal visit if possible. The CTRU is conveniently located adjacent to Stanford/LPCH OB clinic
    - if less than starting hemoglobin, then refer to hematologist

Group 2: (oral iron)

- 4 weeks post-initiation labs to be timed with prenatal care where possible
- Pill count to occur with CTRU or MFM research staff to assess compliance
    - If compliance a concern, assess reasons why

In both groups, patient will complete a survey monitoring symptoms and adverse effects.

7.2 Post Randomization Visits and management of IDA for both groups at 8 weeks

Group 1: (IV iron) Follow up visits
Important for patient to maintain prenatal care, beyond 28 weeks gestation: frequency this is often every 1-2 weeks

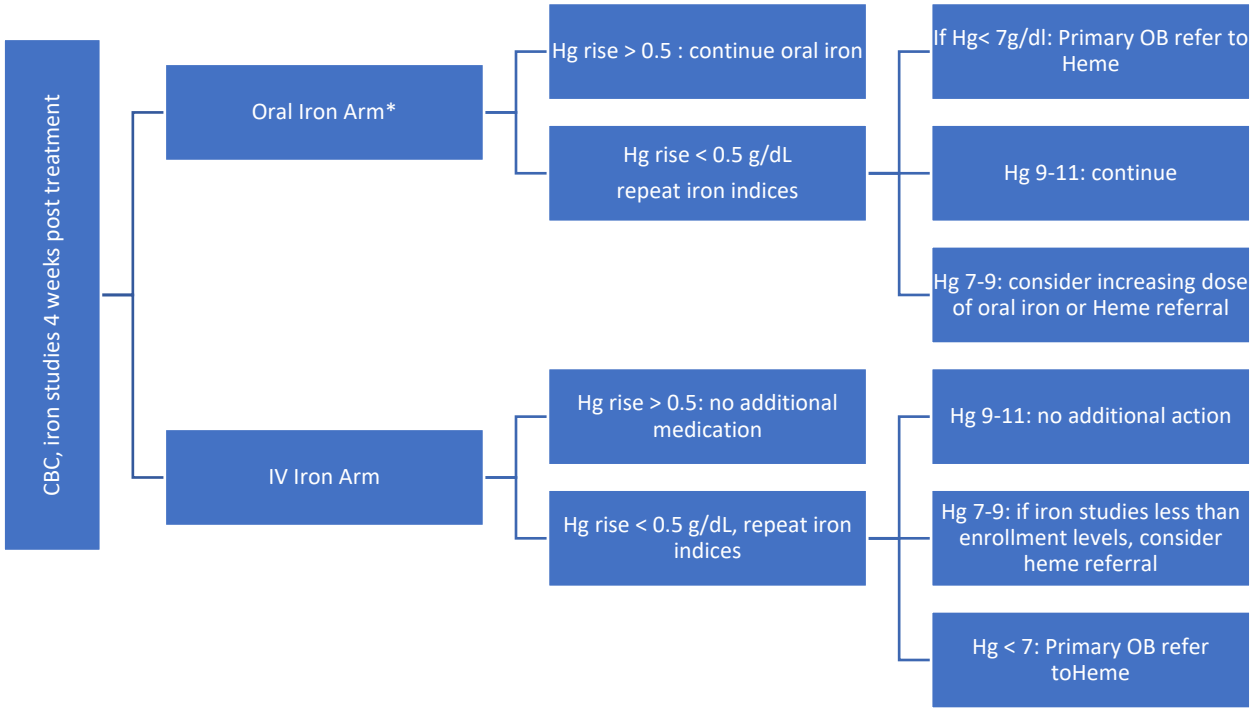
- 8 weeks post-completion treatment labs to be timed with prenatal visit if possible. The CTRU is conveniently located adjacent to Stanford/LPCH OB clinic

Group 2: (oral iron)

- 8 weeks post-initiation labs to be timed with prenatal care where possible
- Pill count to occur with CTRU or MFM research staff to assess compliance
    - If compliance a concern, assess reasons why

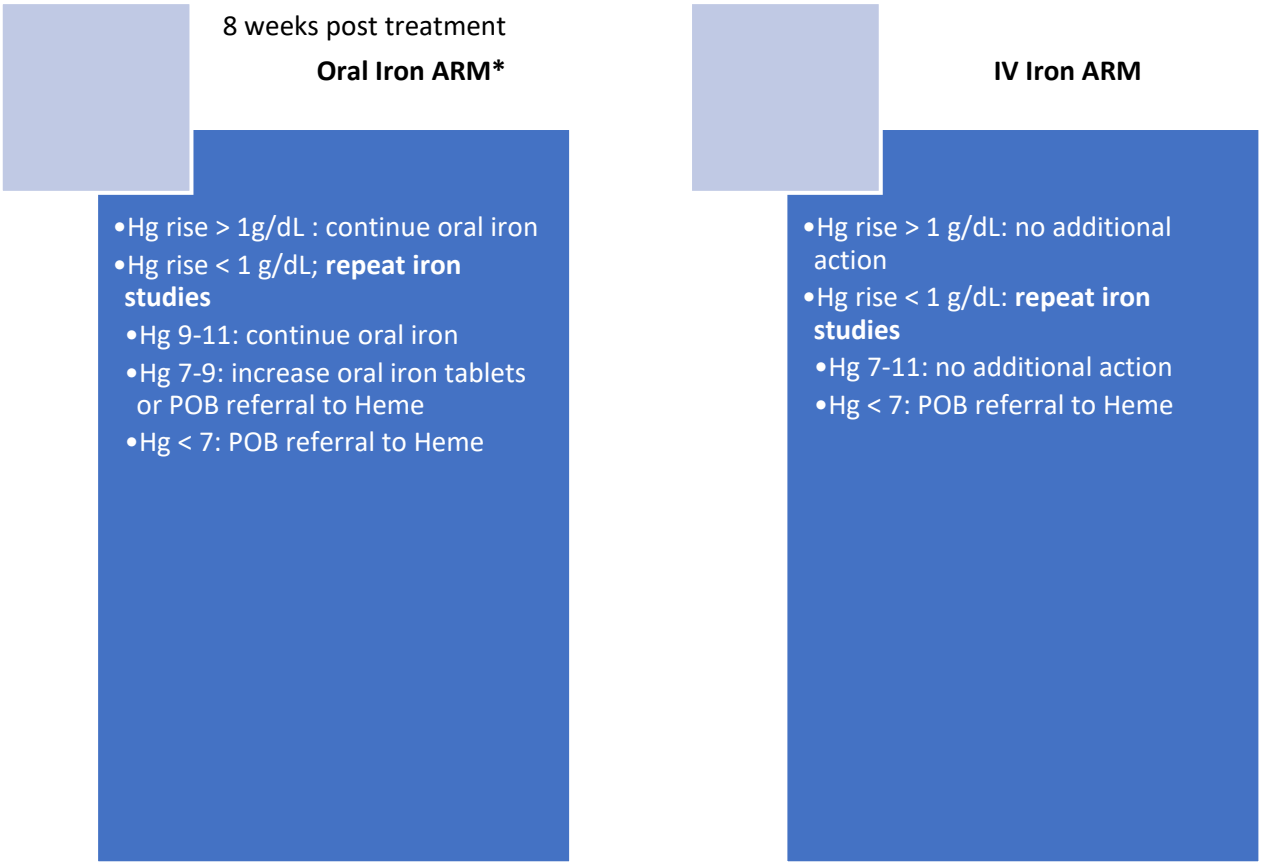
In both groups, patient will complete a survey monitoring symptoms and adverse effects between 8-12 weeks after initiation of therapy.

Algorithm B: Eval for labs post 4 weeks treatment



* Oral arm: if patients state they are intolerant to oral iron at any time during the study – refer to OB to discuss alternative treatment options

Algorithm C: Evaluation of Labs 8 weeks post treatment



*Oral arm: if patients state they are intolerant to oral iron at any time during the study – refer to OB to discuss alternative treatment options

7.3 Management of patient's intolerance to study intervention

Oral iron:

For adverse effects, particularly GI, consideration may be given for IV iron as this is standard of care. Per ACOG, intravenous iron is an approved indication for patient's intolerant of oral iron.

Intravenous iron:

For adverse effects such as hypotension (maternal BP<90/60) and persistent dizziness, headaches, lightheadedness or fatigue and no other potential cause other than the medication, will be assessed for adverse reactions and any signs of anaphylaxis. Methylprednisolone, solumedrol, or dexamethasone, albuterol nebulizers, and intramuscular epinephrine will be available on site for any immediate concerns.

PLEASE REFER TO THE DETAILED ALGORTIHM APPROACH FOR MANAGEMENT OF ADVERSE REACTIONS: this is a figure from Rampton, et a "Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management."

For patients that are stable for transfer, the plan will be for obstetric monitoring and further evaluation at the LPCH OB triage on the third floor. The location is across the street from the CTRU and Stanford/LPCH clinic. The patients will still be followed by the study in intent to treat fashion. In the cases of an unstable patient, 911 will be called and patient will be transferred immediately to the emergency room.

To increase effective management of possible hypersensitivity reactions in the IV group: the following have been included.

- Reference range of normal vitals in pregnancy
- Algorithm for management of hypersensitivity reactions

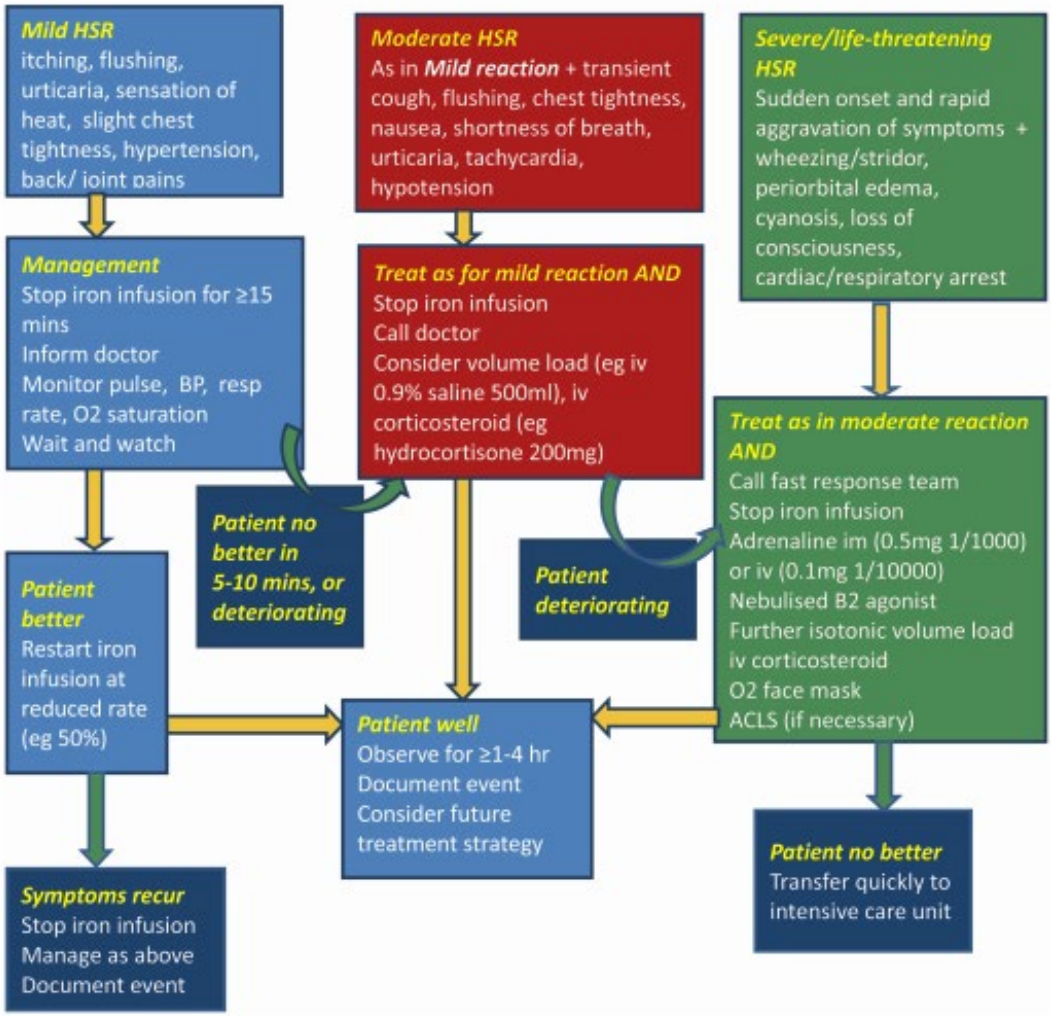


Figure 1. Algorithm outlining grading and management of acute hypersensitivity reactions to intravenous iron infusions. Details are given in the text.

I. Management of mild Hypersensitivity reactions
II. Mild of Moderate Hypersensitivity reactions
III. Severe/life threatening Hypersensitivity reactions

Note: Methyl prednisone prior to IV infusion may considered on case by case basis for patients with history of asthma or high risk medication allergy.

Visit Description	Screening/ Enrollment	Treatment		4 weeks Post-initiation/ Post-completion	8 weeks Post-initiation/ Post-completion	Delivery	1 day Postpartum	6 weeks postpartum
		IV Ferumoxytol	Oral Ferrous sulfate					
Visit Window	24-34 weeks GA	24-34 weeks	24-34 weeks GA up to delivery				1 day after delivery	
Screening of pregnant women with eligible hemoglobin and ferritin levels	X							
Review eligibility criteria	X							
Informed consent	X							
Iron studies with or without baseline complete metabolic panel (depending on history of liver or kidney disease)	X							
Randomization	X							
Assign study number	X							
Demographics	X							
Medical and obstetric history review	X							
Initiate Oral iron study medications			X					
Schedule a visit at the CTRU for IV Iron infusion or coordinate with Antepartum Unit		X						
IV iron infusion appointment, 1st session		X						
Second IV iron infusion, as needed based on initial hemoglobin levels		X						
Monitoring during the IV Iron infusion and post-infusion period		X						
Blood draw to check CBC at 4 weeks after initiation of oral iron/ post-completion of IV infusions				X				
Blood draw to check CBC 8 weeks after initiation of oral iron/ post-completion of IV infusions					X			
Blood draw to check CBC during the time of admission for delivery (SOC)						X		
Blood draw to check hemoglobin, hematocrit level post-delivery (SOC)							X	(per OB)
SAE/ AE monitoring, reporting, recording		X	X	X	X	X	X	X
Pregnancy/ prenatal data collection						X		
Delivery data collection						X	X	
Neonatal data collection						X	X	

7.4 Study Procedures by Visit

Research staff trained in obstetric and perinatal outcomes abstraction will be responsible for research data abstraction from patient medical records. Outcomes will be ascertained until delivery and maternal/infant discharge and up to 6 (4-12) weeks postpartum depending on the outcome.

7.5 Management of Unscheduled Visits

To facilitate appropriate management of study participants during unscheduled visits, we will:

- Prominently display participant status in the patient's EHR for all providers to see
- Include information regarding the management plan that corresponds to the study group
- Provide the patient with brochure that outlines the study group and management algorithm
- Include contact information to allow study staff to be reached as needed for questions.

7.6 Post Randomization Participant Management

Clinical management

- A summary of the research management algorithm for patients in each of the two study groups will be strategically posted at clinic locations and will be placed in each participant's medical record; the patient should have an informational copy of their labs and management algorithm and advised to bring to scheduled and unscheduled visits.
- OB Welch Clinical labs staff will be available to draw labs at 4 and 8 weeks after initiation of therapy: if a patient has Clinical labs that are indicated for any other reason by primary OB, the study labs can be paired with the clinical draw.
- IV iron group will receive additional follow up for adverse symptoms 1 week post infusion and 4 and 8 weeks after initiation of treatment
- Oral iron group will receive survey of symptoms 1, 4, and 8 weeks after initiation of treatment
- Routine pregnancy care at each center will be given to patients by clinical providers trained in the study protocol.
- Ultrasound for anatomy or fluid/growth and antenatal testing will be per clinical center's routine.

7.7 Participant follow up

A clinic visit (preferred method) or follow up call will occur at 6 (4-12 weeks) weeks after delivery in accordance with routine postpartum care. Several data forms will be used during this follow-up process using forms for maternal outcomes, newborn outcomes, NICU outcomes, and 6 weeks follow up forms. These forms, HIPAA compliant, will be entered into the REDCap database.

At randomization, 24-28 weeks (up to 30 complete weeks if necessary) 4 and 8 weeks post-initiation (Oral iron)/ post-treatment (IV iron) labs will be collected as described above. We will also perform chart abstraction to determine hemoglobin levels at the time of admission for delivery and 1 day postpartum (these labs are drawn routinely at LPCH).

In addition to routine prenatal and postpartum clinic visits, participants will be followed up to ascertain maternal and infant status related to re/admissions and ER or unscheduled visits. The records of any ER visits or hospitalizations will be obtained for review.

7.8 Study Drug, Dispensing

Stanford's investigational pharmacy will dispense IV iron infusion to CTRU. CTRU will dispense/administer study infusion(s) to research participant and will provide oral acetaminophen prior to the initiation of IV iron infusion.

Participants receive medication supplies from the outpatient pharmacy. Oral iron tablets will be distributed 100 tablets at a time. Medication dispensing may occur in the intervening periods between visits in case of emergency, loss, or schedule changes. A tracking mechanism is maintained for all dispensing actions.

The participant will report by monitoring survey how many doses were missed. The only reasons that a patient may return the bottle include expired medication or if she does not tolerate the medication and is switched to something else. If the participant doesn't have enough left to supply her until her next visit, she will be dispensed a new bottle and told to complete the current supply and then start the new bottle

7.9 Biospecimens

7.9.1 Maternal Blood Samples will be collected at the following time points (see table below):

- Randomization (at 24-28 weeks age gestational age-optimal) may collect up to 32 weeks
- 4 weeks after post –initiation for oral group or post-completion for intravenous group.
- 8 weeks after treatment post –initiation for oral group or post-completion for intravenous group.
- Delivery*
- Postpartum day 1*

* collected with routine delivery at LPCH. Routine CBC at birth admission and postpartum day 1 with LPCH. This will be in the patient's electronic health record.

8. DELIVERY (including pregnancy loss after randomization) AND POST-DELIVERY

Outcome Data Collection and Chart Review Delivery Outcomes will be ascertained - on an ongoing basis until discharge.
Study personnel will abstract the hospital charts and compete information for REDCap entry:

- Labor and Delivery Data
- Neonatal Outcome Data
- Placental Pathology (review only if sent by primary Obstetrician)
- NICU admission form (if indicated)
- Adverse Event
- Study Intervention Discontinuation and Participation discontinuation/withdrawal

9. PROCEDURES FOR INACTIVE/ LOST/ REFUSED PARTICIPANTS AND MISSED VISITS

9.1 Overview

Staff will use a systematic approach in attempting to recover reluctant participants, i.e., those who have either expressed interest in dropping out of the study or appear to be likely to drop-out due to noncompliance with any aspect of the study.

The goals to avoid drop-out and accomplish drop-out recovery include the following:
1. to ensure that participants are not pushed to the point that they refuse to participate further
2. to continue to engage participants through some form of contact (e.g., phone, e-mail) and allow an opportunity to determine participants' concerns and problem-solve for solutions to concerns and barriers to participation,
3. to foster some form of continued participation (e.g., even an agreement to allow future contact)

The general approach to drop-out recovery will involve contact by the study coordinator in an attempt to:
1. identify barriers to participation
2. problem-solve for solutions to overcome identified barriers
3. apply motivational enhancement methods

In situations where a participant's behavior suggests that she **does not** wish to participate, the participant can be removed from the study.

9.2 Definition of Participant Status.

For purposes of the study, we define the following terms related to trial participation status:

- Active status – active if iron medication therapy is managed according to the study algorithm. There may be instances where a provider is managing the participant's medications in accordance with the study protocol (i.e. many may commonly prescribe oral iron for anemia without iron studies), but the participant is obtaining medications from a (non-study) pharmacy of his/her choosing; in such situations, the participant is considered to be active as well.

- Inactive status –inactive or non-compliant if her iron medication is no longer being managed according to the study protocol with CTRU and she has not withdrawn consent for regular measurement (follow-up) visits or event monitoring is still being performed.

- Lost status –lost-to-follow-up if she has missed several appointments and cannot be contacted by any ordinary means (e.g., home phone, cell phone, mail, email, fax, etc.), clinic staff does not know the participant's whereabouts, and alternative contacts either do not know where the participant is or cannot be contacted themselves.

· Withdrawn/Refused status –participant is considered to be withdrawn if he/she has withdrawn consent to participate in the study and refuses further contact for any reason.

10. ADVERSE EVENT REPORTING

Serious adverse events that meet any of the following criteria:

• fatal or life-threatening
• result in significant or persistent disability,
• require or prolong hospitalization,
• result in a congenital anomaly/birth defect, or
• are important medical events that investigators judge to represent significant hazards or harm to research participants.

Specifically, any AE that meets any of these criteria (maternal death, ICU admission stroke, myocardial infarction, cardiomyopathy, fetal death or neonatal death) will be documented and reported as a SAE.

In addition, any unexpected event/ unanticipated problems which the investigator identifies will be reported.

10.1 Data Safety Monitoring Board

A DSMB will be activated to ensure the safety of participants by analyzing data and to oversee the validity and integrity of the data.

Any serious adverse event or unanticipated problem will be reported to the Stanford IRB. A Data Safety Monitoring Board (DSMB) will be established, with responsibility to monitor all aspects of the study and monitor data and oversee participant safety. DSMB participants include the senior faculty, staff, and representatives from the Stanford Maternal Fetal Medicine Division, Internal Medicine, Hematology and Nephrology. The DSMB will meet once a year to monitor safety, to advise on study progress and performance, protocol modification, or whether there should be early termination.

The outcome of reviews will be relayed to the IRB and protocol director.

10.2 Reporting of Adverse Events

In addition, the following maternal events are examples of adverse events to be reported:
Maternal or perinatal allergic reaction:

- Angioedema, anaphylaxis or generalized skin rash
- Transfer to Chronic Care facility (neonatal)

- Maternal arrhythmia (especially QT prolongation) or congestive cardiac failure (EF<45%)
- Neonatal arrhythmia (especially QT prolongation)
- Any adverse event leading to discontinuation of study medication or suspected to be due to the medication
- Maternal pulmonary thromboembolism
- Maternal admission to ICU
- Neonatal IVH Grade III or IV
- Prolonged maternal or term neonatal hospitalized

11. QUALITY CONTROL

Quality control and assurance are the responsibility of every member of the IDA trial.

All clinic personnel are responsible for understanding the protocol procedures.

Research Staff responsibilities:

- Maintaining the integrity of the protocol and regulatory document binder.
- Developing a data entry system that incorporates real-time data quality assurance features, such as range and logic checks
- Monitoring site initiation requirements.
- Monitoring the screening and randomization processes to ensure randomization of eligible participants and appropriate randomization allocation of participants.
- Generating timely web-based reports describing clinic and study performance, including but not limited to: a) recruitment b) visit adherence and visit completeness c) study intervention) data entry e) data completeness f) outcomes documentation
- Monitoring documentation of 100% of potential outcomes

12. STATISTICAL ANALYSIS

12.1 Statistical Considerations

Efficacy Endpoint(s): The primary outcome for this study is to assess the delta in hemoglobin pre and post intervention in both treatment groups. Our hypothesis is that the rate of increase of intravenous iron will be approximately 1.5g/dL higher in the IV iron cohort versus the oral iron cohort

Secondary Efficacy Endpoint(s): The secondary outcomes for this study include the following:

- correction of anemia at the time of birth hospitalization,
- rates of blood transfusion,

- neonatal outcomes such as APGARs and NICU admissions
- maternal/neonatal infection
- mode of delivery (NTSV)
- infant birth weight

12.2 Sample size determination

We estimated minimum sample size required for 90% power, one-sided α=0.025, and estimated effect sizes for the outcomes of change in proportion of women (Hg <11g/dL) by birth hospitalization based on the findings of previous studies[26,47]. Based on these parameters and allowing for 20% drop-out rate, the study requires 32 subjects per arm. The analysis plan and sample size calculation were developed in consultation with Maternal-Fetal Medicine Senior Biostatistician, Stephanie Leonard, PhD (Co-I). We plan to recruit up to 80 patients to account for potential loss to follow up. We plan to update this sample size calculation based on a pilot study that we are conducting at our institution. We also plan for a much larger sample size in order to conduct analyses stratified by race/ethnicity and to study rare secondary clinical outcomes, as well as possibly compare formulations of intravenous iron, none of which has been done previously.

12.3 Analyses

We will conduct an intent-to-treat analysis to compare the primary and secondary outcomes between the treatment arms. The primary outcome is the mean change in hemoglobin in oral vs IV iron over 4 weeks as well mean change in hemoglobin pre delivery. The primary outcome will be assessed using t-tests. Baseline characteristics between the groups will be compared using t-tests and chi-square tests. If there is an imbalance between the treatment arms, we will use multivariable regression modeling. Differences will be considered statistically significant at $P<0.05$.

13. POTENTIAL CONTINGENCY PLANS

Patient compliance will be assessed in this trial by pill count in the oral arm and by keeping a log of the study infusions in the IV arm. If enrollment is low, we will engage additional obstetric providers whose patients deliver at LPCH such as San Mateo clinic. The IRB revision with the updated formulation ferumoxytol is approved. The goal remains to identify the optimal intravenous iron preparation that combines lowest risk optimal amount of elemental iron with least burden on the patient (fewest visits, short infusion times) with optimal amount of elemental iron.

References

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