**The University of Texas Medical Branch at Galveston**
**Research Protocol # 21-0127**

**Title:** A Feasibility Trial of Intravenous Iron vs. Oral Iron Supplementation for the Treatment of Postpartum Anemia (IVIRONMAN)

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**Funding Sponsor:** Departmental

## 1. Introduction and Purpose:

Postpartum anemia is a major global maternal health problem. In developing countries, postpartum anemia affects more than two thirds of women. In the United States, it affects 50% of mothers (1) and it has been linked to maternal morbidities such as impaired cognition, depression, and fatigue (2-5). Its negative impact on infant-mother bonding and neonatal care (6) has been reported. A major risk factor for postpartum anemia is iron deficient anemia in the antepartum period. The latter results from physiological changes in pregnancy; total blood volume increases by approximately 50% and red blood cell mass increases by 25% (7). The relative increase of blood volume compared to red blood cell mass causes a physiological anemia of pregnancy and therefore the hemoglobin and hematocrit threshold for diagnosing anemia in pregnancy are different than that of a non-pregnant adult. This increase in red blood cell mass, combined with the needs of the fetus, placenta, and normal anticipated blood loss from vaginal delivery represent a total additional need of 1,000 mg iron for a pregnancy, depleting maternal iron reserve (8-11). Oral iron supplementation is currently the standard of care for women with iron deficiency postpartum anemia (12,13). Up to 40% of patients do not tolerate oral iron (13), mainly due to gastrointestinal effects, leading to poor compliance and persistent anemia (14). Intravenous (IV) iron has advantages that bypass absorption challenges and may lead to faster recovery of iron stores and hemoglobin concentrations (11), with a proven safety record (16-17). Despite its advantages, IV iron is more costly and needs to be administered under supervision in a hospital or outpatient clinical setting. Two major reviews have evaluated the impact of IV iron in the postpartum period (18, 19). The first review did not find differences in maternal fatigue or maternal deaths, but did not report hematological effects such as postpartum hemoglobin. Four new randomized trials have been published comparing IV iron to oral iron therapy (20-23). An updated review of 15 randomized control trials (N=2182) concluded that hemoglobin concentrations at 6 weeks postpartum were almost 1 g/dL higher in women who received IV iron compared to oral iron (19). The safety profile of IV iron was also reassuring. Among the 15 trials included, only 2 were from the United States and neither one had 6 weeks postpartum hemoglobin as primary outcome. Hence, a large multicenter clinical trial is needed to adequately assess the impact of both modalities on hematological effects of postpartum anemia. Our aim is to perform a feasibility trial in order to guide a larger definite trial.

Brief Study Design and Rationale

Patients randomly assigned to 2 groups will be compared:

1. **Oral Iron group:** Ferrous sulfate 325 mg (65 mg elemental iron) by mouth for a total of 6 weeks TID.
   1.1 IV placebo in sodium chloride 0.9% 500mL infusion will be given before discharge home over 1.5 hour, preceded by placebo test dose IV infusion of 100mL 0.9% sodium chloride.

2. **IV Iron group:** Low molecular weight iron dextran (infed) 1000mg in sodium chloride 0.9% 500mL IV infusion over 1.5 hour, preceded by test dose of 25 mg IV low molecular weight iron dextran infusion in 100mL 0.9% sodium chloride.
   2.1 Oral placebo will be given by mouth for a total of 6 weeks TID.

The standard of care at UTMB for the detection and treatment of postpartum iron deficiency anemia is as follows. All postpartum patients undergo blood draws at their first postpartum day for anemia screening. Those patients who are identified as anemic (hemoglobin < 12 g/dL) then receive oral iron supplementation. There are many different iron supplements that are used at UTMB to treat iron deficiency in pregnancy. These supplements vary in elemental iron content, enteral coatings, and supplements combined with vitamins and minerals. The choice of which iron supplement is left to the discretion of the provider caring for the patient. Among these choices, ferrous sulfate (325mg, with 65mg elemental iron) is very commonly prescribed to UTMB patients and thus is the oral iron therapy that will be used for this study. Standard UTMB treatment surveillance includes blood draws at the 3 and 6 weeks routine postpartum visits. This study will follow the UTMB standard treatment surveillance protocol and thus study participants will have no study specific blood collections.

Primary outcomes:

- Postpartum hemoglobin and hematocrit at 6 weeks postpartum visit

Secondary outcomes:

- Assessment of adverse effects (such as: arthralgia, backache, chills, dizziness, moderate to high fever, headache, malaise, myalgia, nausea, and vomiting)
- Analysis of CBC indices including reticulocyte count, MCV, etc.
- Iron studies at time of diagnosis (Total Iron binding capacity, Ferritin, serum Iron levels: this panel measures the amount of iron used from the body's stored iron in contrast to reticulocyte counts that measures amount of red blood cells the bone marrow is making).
- Need for transfusion in the peripartum period
- Postpartum hemoglobin and hematocrit
- Neonatal weight
- Postpartum fatigue (multidimensional fatigue inventory (MFI) instrument validated by Smets et al.) at 6 weeks visit.
- Postpartum depression (Edinburgh postnatal depression scale) at 6 weeks visit.
- Neonatal outcomes such as NICU admission, hyperbilirubinemia, and APGAR scores
- Relationship of obesity to effectiveness of supplementation in both study arms
- Drug compliance

Study Risks and Benefits:

The known risks of IV iron therapy are minimal infusion reactions: nausea, vomiting, chills, headache, flushing, constipation, mild arthralgia/myalgia of the chest or flank or facial flushing. All of these symptoms routinely abate after therapy, and plasma tryptase levels drawn after the reaction are always normal. The symptoms are most likely due to minor reactions to labile plasma iron released with any of the formulations. Compared to the side-effects present in the majority of people taking oral preparations, such as constipation, metallic taste, gastric cramping and thick green tenacious stool, the adverse events with IV iron are minor, infrequent and short-lasting. Another concern is anaphylaxis, it

has been reported to be very rare (0.6%) with the new IV iron formulation currently in use. IV iron is consequently moving rapidly forward in the treatment paradigm. Published evidence supports a wider and earlier role for IV iron in the management of postpartum anemia and raises the question of whether it should be frontline therapy in such condition.

**2. Concise Summary of Project:**
This trial will be a comparative pragmatic double blinded feasibility randomized controlled trial of daily versus IV iron in anemic postpartum patients.

Two randomly assigned groups will be compared during the postpartum period:

1. **Oral Iron group:** Ferrous sulfate 325 mg (65 mg elemental iron) by mouth for a total of 6 weeks TID.
   IV placebo in sodium chloride 0.9% 500mL IV infusion will be given before discharge home over 1.5 hour preceded by placebo test dose IV infusion of 100mL 0.9% sodium chloride.

2. **IV Iron group:** Low molecular weight iron dextran (infed) 1000mg in sodium chloride 0.9% 500mL IV infusion over 1.5 hour preceded by test dose 25 mg IV low molecular weight iron dextran infusion in 100mL 0.9% sodium chloride.
   2.1 Oral placebo will be given by mouth for a total of 6 weeks TID.

The number of subjects studied will be 40 at UTMB, we plan to approach and consent up to 40 patients to allow for screening failures, early withdrawals, and patients lost to follow-up, and patients who must withdraw due to failure of therapy. This number was decided for the aim as a feasibility trial goal. Study to last an anticipated length of 1 year. If our sample size is not achieved by that time, we will consider the trial as not feasible at UTMB only. This trial will provide important information such as eligibility, consent, and outcomes rates on which to base feasibility and sample size calculations for a larger definitive trial, as well as how many clinical sites would be needed.

**3. Study Procedures:**
Patient Population
The patient population will be selected from obstetric patients who delivered at UTMB health system. This population can broadly be divided into patients cared for by one of the UTMB faculty obstetric providers and those who receive care through the Regional Maternal and Child Health Program (RMCHP). We anticipate that the majority of the patients in this study will be recruited from the RMCHP patients.

Locations
John Sealy hospital will be our recruitment site. Research staff will be present at the location and consenting and enrolling will only occur when research staff are present.

Research Team
The research team (or research staff) will consist of the PI, trained research coordinator, and additional staff to be trained and added to the research protocol. All members of the research team will be able to screen and consent subjects. The PI will work to ensure that the team is of sufficient size to carry out the project. Consenting and enrollment of subjects will only occur when a research team member is physically present at the study location.

Screening

All pregnant patients who deliver in our unit undergo a laboratory screen for anemia at the first postpartum day as part of the UTMB standard of care while recovering in the hospital. Eligible patients (PPD#1 patients with a hemoglobin less than 9 g/dl) will be screened and approached while inhouse (detailed under section 8).

The anticipated procedures flow is as follows

1. Research staff will go to postpartum ward.
2. Research staff will confirm with provider that possible subjects are appropriate candidates for treatment with ferrous sulfate.
3. Research staff will approach screened patients to obtain consent from possible subjects.
4. Subjects will be randomized using a computer-generated sequential randomization log with group assignment, subject name, and medical record number.
5. After patient is consented and enrolled, the provider will be notified orders will be placed in EPIC by providers with the assistance of the research staff; and a note will be placed in the electronic chart indicating that the patient is enrolled in the study.
6. Subjects will continue to receive standard, routine postpartum care and surveillance of postpartum iron anemia.
    a. Research staff and PI will periodically monitor surveillance data by chart review.
7. During their routine 6 weeks postpartum visit, patient's hemoglobin level will be obtained (standard of care at UTMB). If subjects have a hemoglobin level drawn before the 6 weeks visits, such as in the 3 weeks postpartum visit, we will also collect this information.
8. Research staff will conduct chart review to obtain the data points for the primary and secondary outcomes (described in section 1)

Additional details

Our primary outcome as well as secondary outcomes are convenient data points collected in the standard treatment and surveillance of postpartum anemia. As such patients will not need any study specific venipuncture or visits. The frequency and availability of appointments ensures that any symptomatic patient will quickly be seen and evaluated.

Any subject who requires escalation of treatment beyond oral or IV supplementation (blood transfusion) will be referred to receive appropriate intervention. These subjects will still be included in the intent-to-treat analysis. The routine surveillance of anemic postpartum patients described above ensures that any treatment failure will be quickly identified and addressed.

Outcomes

Our primary outcome will be hemoglobin level at 6 weeks postpartum. Based on the available evidence we hypothesize that IV iron supplementation will be superior or at least not inferior to oral iron supplementation. Additionally, we aim to assess the secondary outcomes as listed in the introduction obtained by chart review. Data to be collected includes population characteristics including demographics and data points described in the outcomes listed under the introduction obtained by chart review.

**4. Disposal and Administration of Drug and Placebo/Drug compliance**

The intervention drugs (IV/PO Iron and placebo) will be provided by Greenpark Compounding Pharmacy and UTMB Investigational Drug Service (IDS). The latter will receive, store and dispense the drugs for the study.
Once a qualified subject is consented and randomized, an order will be entered in Epic. The UTMB IDS will be notified to dispense the study drug according to the treatment assignment per study protocol. The assigned drug and placebo will be delivered to the nursing unit to be administered by the nurse assigned to the subject. The assigned nurse will document the administration in Epic using Medication Administration Record (MAR). Any unused study drug will be returned to IDS for documentation and disposal. Medications used in this study will not be billed to the subject or her insurance company.
The IDS will dispense the pills in a container/bottle and the subject will be given the bottle and given instructions to come to clinic at 6 weeks postpartum to see provider with bottle/container. The supplies given will be enough for total treatment of 6 weeks.

The subject will be included in the analysis by intent-to-treat once the assigned pills are dispensed from IDS and sequential number posted on the subject specific randomization form.

Drug compliance: subject will be instructed to bring pill container to all clinic visits. The provider will document number of pills in the container in order to account for compliance at best in each postpartum visit and emphasize compliance. At the end of the treatment period (6 weeks postpartum visit), the research team will collect the container and count the returned pills prior to returning it to the IDS for reconciliation within 2 weeks of receiving the bottle. Study participation will end at 6 weeks postpartum. However, if subject does not come to their scheduled postpartum visits, we will do our best to attempt to contact and retrieve drug container up to 10 weeks postpartum.

If subject misses her regular postpartum visit, we will make every effort to contact the subject by phone and enquire about the outcomes.

**5. Criteria for Inclusion of Subjects:**

- Maternal age ≥ 18 years and < 50 years
- Delivery at UTMB
- Hemoglobin below 9 g/dl in postpartum day 1: This population has the highest risk to have complications from postpartum anemia, protracted recovery and the most to benefit from IV iron (4 studies showed benefit of IV iron at 6 weeks PP in subjects with baseline hemoglobin values ranging from 7.4 to 8.1 g/dL.)[19]
- Singleton gestation

**6. Criteria for Exclusion of Subjects:**

- Enrolled in another trial that may affect outcome at the discretion of the PI
- Diagnosis of malabsorptive disorder or history of gastric bypass procedure
- Known diagnosis of anemia other than iron deficiency (thalassemia, macrocytic anemia, sickle cell, etc.)
- Significant cardiovascular disease, including but not limited to myocardial infarction or unstable angina within 6 months prior to study inclusion or current history of NYHA Class III or IV congestive heart failure
- Patient has received blood transfusion or there is a plan to transfuse
- Lactose intolerance

## 7. Sources of Research Material:

The primary and secondary outcomes for this trial will be obtained from chart review for enrolled patients.

## 8. Recruitment Methods and Consenting Process:

Patients delivered at UTMB Galveston campus will be screened to identify patients with a hemoglobin below 9 g/dl in postpartum day 1 who also satisfy the other eligibility criteria. Clinical providers will be educated about the trial prior to enrollment. We plan to identify these patients by screening the charts of patients delivered in our labor and delivery unit to identify potential subjects. Information to be reviewed as part of the screening process will be hemoglobin laboratory data and relevant exclusion and inclusion history. Research staff will function as the screeners and will alert providers that their patient is a potential subject. The provider caring for that patient will then be informed of the patient's eligibility. Research staff will work with the provider to ensure that the study intervention is appropriate therapy for the patient. If the provider agrees that the study intervention is appropriate, the provider will then approach the patient to ascertain interest in participation. If the patient is interested, the provider will introduce the research staff to the patient who will then explain the study to the patient as part of the consenting process. A screening log will be used to track all subjects approached for the study. At the time of consent and randomization, the patient will be educated as to the dosing regimen as well as the routine treatment surveillance that will occur. This will be done by the research staff consenting the patient.

Spanish speakers:

Spanish speaking patients will be screened by use of a Spanish interpreter and all patient study materials will be translated into Spanish.

Consenting process:

Written consent will be obtained in a private room in the hospital postpartum ward by direct person-to-person conversation. The PI or a collaborator will be responsible for the informed consent. Subjects will be given the time needed in order to fully understand and read the consent forms up to 12 hours. All efforts will be made by the research staff to answer all questions the subject has and to ascertain that the subject has the right to refuse to participate in the study. The consent form and process will describe that patients will be randomly assigned to either the study or control group. Each patient will be informed that participation is completely voluntary and in no way will affect the postnatal care they receive.

## 9. Potential Risks:

Randomization Risk:

Since treatment will be randomized, it is possible that one or more of the other treatment groups will have more benefit or lower side effects than the other group.

Loss of Confidentiality:

Any time information is collected, there is a potential risk for loss of confidentiality. Every effort will be made to keep the subject's information confidential; however, this cannot be guaranteed.

Blood Draw Risk:

Each subject will have two blood draws collected throughout their participation in the study. Risks of taking a blood draw include pain, a bruise at the point where the blood is taken, redness and swelling of the vein, and infection. There is a rare risk of fainting. These blood draws are part of the standard of care and will not place study subjects at any additional risk.

IV Placement Risk:

Each subject will receive IV Iron or placebo based of randomization group. Risks of IV placement are possible pain, bruising, and infection at the site of the needle stick where the IV is placed. Anxiety (nervousness) may possibly be experienced during the placement of the IV.

**10. Subject Safety and Data Monitoring:**
The PI and research coordinator will be responsible for monitoring the safety of this study, this will occur on a quarterly basis. The monitoring will include participant demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, summary of adverse events (AEs) or serious adverse events (SAEs) which may have occurred. AEs and SAEs will be reported per IRB policies.

**11. Procedures to Maintain Confidentiality:**
Data collection will be identified with a participant ID number. Data will be collected and stored with the participant ID code only. The master enrollment log linking subject identifiers with study ID numbers will be kept in a password-protected database. Relevant data variables (specified under outcomes) will be collected by chart review and placed into an Excel or Access file. These files will not contain identifiable information and will be stored in password protected, secured UTMB servers. The research coordinator and PI will be available to monitor the data and correct any discrepancies based on source documents if needed.

**12. Potential Benefits:**
The potential benefits of the study to the intervention group (IV iron) include:

1. Improved fractional absorption of iron with corresponding improvement of anemia compared to standard oral iron replacement therapy
2. Decreased GI side effects with IV iron
3. Faster increase in hemoglobin

**13. Biostatistics:**
We hypothesize that the IV iron group will have a higher hemoglobin level at 6 weeks postpartum compared with the oral group. The primary analysis will be conducted on an intention-to-treat basis. Between-group differences in continuous variables will be assessed using Student t test or Man-Whitney rank sum test and results will be given as mean, standard deviation or median range as appropriate. Categorical variables will be assessed using the Pearson chi-square test or Fisher exact test as appropriate. For dichotomous endpoints, relative risk (RR) and 95% CI values will be calculated. P <0.05 will be considered significant. The analysis will be performed after study completion.
Based on data from the literature[19], we estimate that women who received oral iron will have a mean 6 week postpartum hemoglobin of 11.2 g/dL with a standard deviation of 1.2. We anticipated that women that receive IV Iron will have a postpartum 6 weeks mean hemoglobin of 12.4 g/dL. Using calculated effect size, power of 80% and 2-sided alpha of 0.05, we estimate that we will need 38 (19/group) subjects with complete ascertainment. Accounting for 5% lost to follow up, the final sample size would be **40**.
We will be performing a superiority approach. Stata 16 will be used for the statistical analysis.

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t tests - Means: Difference between two independent means (two groups)

Analysis:   A priori: Compute required sample size
Input:      Tail(s)                        =   Two
            Effect size d                  =   0.9592329
            α err prob                     =   0.05
            Power (1-β err prob)           =   0.8
            Allocation ratio N2/N1         =   1
Output:     Noncentrality parameter δ      =   2.9565544
```

```
Critical t                      =   2.0280940
Df                              =   36
Sample size group 1             =   19
Sample size group 2             =   19
Total sample size               =   38
Actual power                    =   0.8203999
```

**References**


1. Milman N. Postpartum anemia I: definition, prevalence, causes, and consequences. Ann Hematol 2011;90:1247–53.
2. Gaynes BN, Gavin N, Meltzer-Brody S, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ) 2005;119:1–8.
3. Corwin EJ, Murray-Kolb LE, Beard JL. Low hemoglobin level is a risk factor for postpartum depression. J Nutr 2003;133:4139–42.
4. Lee KA, Zaffke ME. Longitudinal changes in fatigue and energy during pregnancy and the postpartum period. J Obstet Gynecol Neonatal Nurs 1999;28:183–91.
5. Beard J, Hendricks M, Perez E, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. J Nutr 2005;135:267–72.
6. Murray-Kolb LE, Beard JL. Iron deficiency and child and maternal health. Am J Clin Nutr 2009;89:946s–50s.
7. ACOG Practice Bulletin 95: Anemia in Pregnancy. 2008.
8. Milman N. Postpartum anemia I: definition, prevalence, causes, and consequences. Ann Hematol 2011;90:1247–53.
9. Butwick AJ, Walsh EM, Kuzniewicz M, Li SX, Escobar GJ. Patterns and predictors of severe postpartum anemia after cesarean section. Transfusion 2017;57:36–44.
10. Wagner KS, Ronsmans C, Thomas SL, et al. Women who experience obstetric haemorrhage are at higher risk of anaemia, in both rich and poor countries. Trop Med Int Health 2012;17:9–22.
11. Milman N. Postpartum anemia II: prevention and treatment. Ann Hematol 2012;91:143–54.
12. World Health Organization. WHO Guideline: Iron supplementation in postpartum women. Geneva: World Health Organization, 2016. Available at: http://apps.who.int/iris/handle/10665/249242. Accessed Oct 15, 2020.
13. Munoz M, Pena-Rosas JP, Robinson S, et al. Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. Transfus Med 2018;28:22–39.
14. Friedman AJ, Shander A, Martin SR, et al. Iron deficiency anemia in women: a practical guide to detection, diagnosis, and treatment. Obstet Gynecol Surv 2015;70:342–53.
15. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. Am J Clin Nutr 2015;102:1585–94.
16. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous
iron preparations: systematic review and meta-analysis. Mayo Clin Proc 2015;90:12–23.
17. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet 2016;387:907–16.
18. Markova V, Norgaard A, Jorgensen KJ, Langhoff-Roos J. Treatment for women with postpartum iron deficiency anaemia. Cochrane Database Syst Rev 2015:CD010861.

19. Sultan P, Bampoe S, Shah R, Guo N, Estes J, Stave C, Goodnough LT, Halpern S, Butwick AJ. Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019 Jul;221(1):19-29.e3.
20. Damineni S, Thunga S. IV ferric carboxymaltose vs oral iron in the treatment of postpartum iron deficiency anaemia. J Clin Diag Res 2016;10:QC08–10.
21. El Khouly NI. Comparison of intravenous ferrous sucrose and oral ferrous sulphate in treatment of postpartum iron deficiency anemia. J Matern Fetal Neonatal Med 2017;30:967–71.
22. Holm C, Thomsen L, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial. Vox Sang 2017;112:219–28.
23. Rathod S, Samal SK, Mahapatra PC, Samal S. Ferric carboxymaltose: a revolution in the treatment of postpartum anemia in Indian women. Int J Appl Basic Med Res 2015;5:25–30.