The University of Texas Medical Branch at Galveston
Research Protocol # 20-0068

Title: A Randomized Trial of Intermittent Oral Iron Supplementation vs. Daily Oral Iron Supplementation for the Treatment of Anemia in Pregnancy

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1. Introduction and Purpose:

Anemia in pregnancy affects 18-21% of pregnant women in the United States and is associated with low birth weight, preterm delivery, and perinatal mortality as well as a possible association with postpartum depression and poor mental and psychomotor performance testing of offspring. Current treatment of iron deficiency anemia in pregnancy consists of daily iron supplementation with the intent of raising hemoglobin back to normal ranges. A recent review examining misconceptions in the management of iron deficiency described the misconception of high dose daily iron supplementation noting, "low daily doses (e.g. 50 mg) or moderate doses (e.g. 100 mg) every other day may increase both tolerance and efficacy of oral iron supplementation" (1). Further commentaries call for continuing research into every other day dosing (2). Given the prevalence and complications of iron deficiency anemia in pregnancy, we propose to study if alternate day dosing of oral iron supplementation is statistically superior or at least not inferior to daily dosing in raising third trimester hemoglobin.

Brief Study Design and Rationale

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

1. Control Group: standard of care, daily oral iron supplementation of ferrous sulfate 325 mg (65 mg elemental iron) taken by mouth once daily.
2. Intervention Group: alternate day dosing oral iron supplementation of ferrous sulfate 650 mg (130 mg elemental iron) taken by mouth every other day.

Historically twice or thrice daily oral iron supplementation has been the recommended as the first line treatment of iron deficiency anemia. This standard of care for oral iron therapy is starting to change (1, 2) with some current textbooks and guidelines recommending either daily or every other day dosing regimens (3, 4). The standard of care at UTMB for the detection and treatment of iron deficiency anemia is as follows. All pregnant patients undergo blood draws at their first appointment for anemia screening. Those patients who are identified as anemic then undergo further studies to determine the type of anemia. Those patients determined to have iron deficiency anemia 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 that patients receive 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 least every trimester or more frequently based on symptomatology of patient and provider discretion. This study will follow the UTMB standard treatment surveillance protocol and thus study participants will have no study specific blood collections. As part of this standard surveillance if hemoglobin levels remain low patients may be considered for more aggressive treatments such as IV iron infusion or transfusion. The decision to escalate treatment takes into account risk of cesarean delivery and risk of obstetric hemorrhage among other considerations and will be left to the discretion of the provider.

Primary outcomes:

- Change in hemoglobin and hematocrit in the 3rd trimester

Secondary outcomes:

- Assessment of GI adverse effects determined by survey
- Analysis of CBC indices including reticulocyte count, MCV, etc.
- Iron studies at time of diagnosis
- Need for parental iron supplementation
- Need for transfusion in the peripartum period
- Postpartum hemoglobin and hematocrit
- Neonatal weight
- Presence of antepartum fetal growth restriction
- Neonatal outcomes such as NICU admission, hyperbilirubinemia, and APGAR scores
- Relationship of obesity to effectiveness of supplementation in both study arms

Study Risks and Benefits:
The known risks of oral iron therapy are gastrointestinal upset such as nausea and vomiting, constipation, and abdominal pain. Oral iron supplementation for the treatment of iron deficiency anemia in pregnancy is the standard of care and as such has been demonstrated to be a safe and effective treatment. Studies have demonstrated that intermittent dosing of oral iron can result in increased iron absorption, however this has not been studied in a pregnant population (5, 6).

2. Background:
The prevalence of iron deficiency anemia (IDA) in reproductive aged women aged 20-49 years is estimated to be 9.2% (7). In pregnancy, rates of anemia affect between 18-21% of pregnant women in the United States with non-Hispanic blacks and teenage mothers affected at even higher rates (8, 9). Outside of pregnancy anemia has been estimated to account for 8.8% of global disability (10). However, during pregnancy IDA has been associated with increased risk of low birth weight, preterm delivery, and perinatal mortality as well as a possible association with postpartum depression and poor mental and psychomotor performance testing of offspring (8). Gabbe et al. notes that "In developing nations, severe anemia is alarmingly common and is a major cause of maternal morbidity and mortality" (11). Pregnant patients with anemia are at further risk for blood transfusion in the event of postpartum hemorrhage.

In pregnancy, hematology physiology changes drastically. Total blood volume increases by approximately 50% and red blood cell mass increases by 25% (8). The relative increase of blood volume compared to red blood cell mass causes a physiologic anemia of pregnancy and therefore the hemoglobin and hematocrit threshold for diagnosing anemia in pregnancy are different than that of a non-pregnant adult (8). 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. It is therefore, unsurprising that the most common etiology of anemia in pregnancy is iron deficiency, representing 75% of all anemia in pregnancy (11).

The World Health Organization (WHO) recommends that pregnant women take 60 mg elemental iron daily while noting that 30 mg might be sufficient (12, 13). The American College of Obstetrics and Gynecology (ACOG) however notes that, "It is unclear whether iron supplementation in well-nourished pregnant women who are not anemic affects perinatal outcomes" (8). Most pregnant women receive some level of iron supplementation through the administration of prenatal vitamins.

The definitive diagnosis of iron deficiency should be made with measurement of serum iron, ferritin, and transferrin saturation; however, recent iron therapy and extended periods of anemia can complicate the interpretation of these results (11). The diagnosis of iron deficiency is often presumed in pregnant patients with

a hemoglobin below 11 g/dl in the first trimester and/or 10.5 g/dl in the second trimester and iron therapy is often empirically started without first obtaining iron studies (8).

For iron deficient anemic individuals, the current recommendation for treatment by the CDC is oral supplementation of 60-120 mg of elemental iron daily (14). However this regimen is being questioned with some sources recommending every other day dosing (3, 4, 15). Ideally response to supplementation should be seen in about 3 weeks in a non-pregnant patient (16). In pregnancy response of an anemic patient to oral iron therapy should be seen with reticulocytosis after 3-10 days and hemoglobin should begin to increase within one week (11, 17). Iron stores however may take 1 month or longer to replenish (11, 18). Of note, obese patients have been found to have decreased iron stores thought to be secondary to an inflammatory response from obesity and increased levels of Hepcidin (19).

While generally considered safe, oral iron supplementation can be commonly associated with adverse gastrointestinal complaints including metallic taste, nausea, vomiting, heartburn, epigastric pain, diarrhea, and constipation (20).

Early studies have begun to question the effectiveness of daily iron supplementation in IDA. Internationally, studies conducted in Malawi (2000) and China (1996) for anemic and non-anemic pregnancy women demonstrated no difference between outcomes (21, 22). A 2015 Cochrane review examined intermittent iron supplementation in anemic concluded that there was no benefit to intermittent supplementation, however this review was limited by a small number of poor quality studies included in the meta-analysis (23). Faced with the obvious limitations of these studies, a more systematic investigation into the physiology and biochemistry of oral iron supplementation was then described. The absorption of iron is a tightly regulated process with hepcidin, the principal iron regulatory hormone, functioning to inhibit iron absorption in the gut (20, 24). In pregnancy, hepcidin levels have been demonstrated to be lower (25). In response to elevated iron stores, hepcidin levels increase thereby inhibiting further systemic iron absorption (26). Recent data has described that oral iron supplementation can increase hepcidin levels as well. In 2015, a study demonstrated that after oral iron supplementation of 60 mg elemental iron or greater, hepcidin levels increased for the next 24 hours which in turn decreased the fractional iron absorption (27). A follow-up study in non-anemic, iron deficient women demonstrated that the inhibitory effect of hepcidin on daily iron dosing could be overcome with single day dosing on alternate days with increased cumulative iron absorption in the alternate day dosing group (6). This study was further strengthened with a similar trial, this time in iron-deficient, anemic women which demonstrated that alternate day of 100-200 mg elemental iron resulted in higher fractional iron absorption with lower GI side effects when comparted to daily dosing (5). Based on studies such as these, some experts have suggested the current treatment of iron therapy may be incorrect, and that alternate day dosing might be beneficial, though further studies are needed (1, 2, 4, 16, 20, 28). Several similar studies are currently in process at this time, links listed in the references section (29-32).

3. Concise Summary of Project:

This trial will be a comparative pragmatic open label randomized controlled trial of daily versus alternate day dosing of oral iron in anemic pregnant patients.

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

1. Control Group: standard of care, daily oral iron supplementation (325 mg PO daily ferrous sulfate)
2. Intervention Group: alternate day dosing oral iron supplementation (650 mg PO every other day ferrous sulfate)

325mg Ferrous sulfate is a standard oral iron supplement providing 65 mg of elemental iron per dose. Standard dosing recommendations for the treatment of iron deficiency anemia is between 65 to 200 mg elemental iron daily.

Each group will receive a phone survey 2-4 weeks after initiation of therapy to assess side effects of each group as well as compliance. Call is anticipated to last approximately 10-15 minutes. This survey has previously been validated in assessing gastrointestinal symptoms for those taking oral iron supplementation (33).

The number of subjects studied will be 86 subjects at UTMB, we plan to approach and consent up to 96 patients to allow for screening failures, early withdrawals, and patients lost to follow-up, and patients who must withdraw due to failure of therapy. Failure of therapy for the purposes of this study will be patients who require parental iron supplementation or transfusion. Study to last an anticipated length of 3 years. If our sample size is not achieved, we will submit to the IRB an addendum to increase the number of consented subjects to achieve the desired sample size.

4. Study Procedures:

Patient Population

The patient population will be selected from obstetric patients receiving prenatal care in the 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

All RMCHP clinics locations will be possible recruitment sites, however we anticipate that the bulk of the recruitment will occurs at the Galveston, Pasadena, and Angleton clinics were the PI and perinatal research division staff are frequently located. Research staff will travel to each clinic 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, faculty sponsor, 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. Physician research team members will be responsible for providing the prescriptions to patients who agree to take part in this study. The PI and faculty sponsor will work together 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 a study location.

Screening

All pregnant patients undergo a laboratory screen for anemia at the first prenatal appointment as part of the UTMB standard of care. Eligible patients (1st or 2nd trimester patients with a hemoglobin below 11 g/dl or 10.5 g/dl respectively) will be screened and approached at their next prenatal appointment for consent (detailed under section 9). We request a waiver to screen these patients.

The anticipated procedures flow is as follows

1. Research staff will travel to location
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 randomization log with group assignment, subject name, and medical record number
    a. Daily dosing group will take ferrous sulfate 325 mg (65 mg elemental iron) by mouth daily
    b. Alternate day dosing group will take ferrous sulfate 650 mg (130 mg elemental iron) by mouth every other day
5. Prescriptions for the appropriate regimen will be provided by the research staff
    a. If the research staff is a physician, the appropriate prescription will be sent at time of encounter
    b. If the research staff is a non-physician, a physician research staff member will be alerted and the appropriate prescription will be sent on the same day
6. After patient is consented and enrolled, the provider will be notified and a note will be placed in the electronic chart indicating that the patient is enrolled in the study.

7. Subjects will continue to receive standard, routine prenatal care and surveillance of iron deficiency anemia in pregnancy
    a. Research staff and PI will monitor surveillance data by chart review
8. 2-4 weeks after initiation of respective iron regimen research staff will contact subjects by phone to administer a 5-10 min survey to assess GI side effects and compliance with regimen.
9. Research staff will conduct chart review to obtain the datapoints for the primary and secondary outcomes (described in section 1)

Survey Details

2-4 weeks after randomization, the patient will receive a phone call from a member of research staff to conduct a brief 5-10 min survey to assess gastrointestinal side effects of iron supplementation and compliance. Patients will be made aware of this survey in the consenting process. Study subjects will then resume standard prenatal care visits.

Additional details

The routine prenatal visits for pregnant patients with anemia include at least monthly venipunctures to monitor the treatment of anemia and intervene if necessary. Our primary outcome of 3rd trimester hemoglobin as well as laboratory secondary outcomes are convenient data points collected in the standard treatment and surveillance of anemia in pregnancy. As such patients will not need any study specific venipuncture or visits. Prenatal visits are frequent with monthly visits in the 1st trimester, bi-monthly visits in the 2nd trimester, and weekly visits in the 3rd trimester with 24 hour after hours care phone services available. The frequency and ready availability of appointments ensures that any symptomatic patient will quickly be seen and evaluated.

Any subject that requires escalation of treatment beyond oral supplementation (IV iron infusion or 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 pregnant patients described above ensures that any treatment failure will be quickly identified and addressed.

Outcomes

Our primary outcome will be change in hemoglobin and hematocrit in the 3rd trimester. Based on the available evidence with hypothesize that alternate day dosing of oral iron supplementation will be superior or at least not inferior to daily 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. A detailed explanation of the analysis of the primary outcome is described in a later section.

5. Sub-Study Procedures:

Not applicable

6. Criteria for Inclusion of Subjects:

- Maternal age ≥ 18 years and <50 years
- Prenatal care provided at UTMB
- Hemoglobin below 11 g/dl in the first trimester and/or 10.5 g/dl in the second trimester
- Microcytic anemia
- Singleton gestation

7. 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.)
- History of cardiopulmonary disease

- Severe anemia of requiring transfusion or parental iron at time of randomization

8. Sources of Research Material:
The primary and secondary outcomes for this trial will be obtained from chart review for enrolled patients.

9. Recruitment Methods and Consenting Process:
Patients receiving prenatal care at the UTMB/RMCHP clinics will be screened to identify patients with a hemoglobin below 11 g/dl in the first trimester and/or 10.5 g/dl in the second trimester who also satisfy inclusion and exclusion criteria. RMCHP clinical providers will be educated about the trial prior to enrollment. We plan to identify these patients by screening the charts of patients scheduled in clinic 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 has interest, the provider will introduce the research staff to the patient who will then explain the study 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 and surveys will be translated into Spanish.

Consenting process:
Written consent will be obtained at the follow up visit by direct person-to-person conversation. The PI or a collaborator will be responsible for the informed consent. Subjects will be given time needed in order to fully understand and read the consent forms. All efforts will be made by the research staff to answer all questions the subject has and to ascertain that subjects have 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 prenatal care they receive.

10. 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.

Persistence of anemia
The every other day dosing group receives iron less frequently than the daily iron dosing group. This could cause an increased risk of persistence of anemia as the every other day dosing may not work as well as every day dosing.

11. Subject Safety and Data Monitoring:
The PI and research coordinator will be responsible for monitoring the safety of this study. Details of monitoring submitted separately.

12. 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.

13. Potential Benefits:

The potential benefits of the study to the intervention group (alternate day dosing) 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 alternate day dosing

14. Biostatistics:

We hypothesize that the intervention group will have a higher hemoglobin level in the third trimester than the standard 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 our historical data at our center of 56 anemic women with iron deficient anemia that received standard daily iron supplementation: third trimester hemoglobin mean of 10.27 ± 1 g/dL. We will first do a noninferiority approach. If noninferiority is not met, we will do a superiority analysis. For the noninferiority: If there is truly no difference between the standard and experimental treatment, then 68 subjects will be required to be 90% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of -1. For the superiority: We estimate that a minimum sample of 39 per group, total N= 78 women will be needed to provide a power of 90% with a two-sided alpha level of 0.05 and a 1 g/dL difference in hemoglobin between control and intervention. We plan to enroll 86 patients in order to account for up to 10% missing data or loss to follow up. If no differences are noted among groups (non inferiority hypothesis failed) we will be performing a superiority approach. Stata 16 will be used for the statistical analysis.

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