**TITLE: IRON DEFICIENCY ANEMIA**

**Subtitle: Treatment of iron deficiency anemia in pregnancy**

**SUMMARY:** The CDC recommends iron supplementation starting in the first trimester to meet the iron requirements of pregnancy. The treatment of iron deficiency anemia (IDA) with oral preparations in pregnancy may be improved by alternate day dosing and lower iron doses then previously recommended. When IV therapy is needed, data now support the use of higher iron doses, administered more rapidly.

**Rationale:** The choice of iron compound and the route of administration are largely dependent on the presence and degree of anemia, reversibility of the underlying cause, clinical status (age, sex, longstanding vs recent onset), and in some instances, patient preference. Iron salts such as iron sulfate, fumarate, and gluconate remain a mainstay of therapy in absolute iron deficiency. The alternative for patients who are intolerant or unresponsive to oral compounds is IV iron. This route of administration is currently more widely used than in the past as a result of the improved safety profile of last-generation compounds. Common established indications for IV iron in pregnancy are reduced absorption capacity in the presence of gastrointestinal disorders (eg Crohn’s dz) or bariatric surgery, severe anemia (Hb <7-8 g/dL), lack of response to oral iron after 4 weeks of therapy, need for rapid hgb increase in 3rd trimester of pregnancy.

**Eligible patients:** The Centers for Disease Control and Prevention (CDC) recommends screening for iron deficiency anemia in pregnant people and providing appropriate treatment. (See toolbox document ANEMIA: DIAGNOSIS of IRON DEFICIENCY IN PREGNANCY for more information).

**Contraindications:**

**-**Pregnant people with genetic conditions such as hemochromatosis should not receive universal iron supplementation.

-Acute hypersensitivity reaction including wheezing, stridor, hypotension, tachycardia, tachypnea or periorbital/angioedema in response to prior IV iron infusion.

**Technique:** **ORAL IRON**

Mounting evidence indicates that low oral doses are more effective and better tolerated than the traditionally recommended 100 to 200 mg of elementary iron per day. **Changing the administration from daily to alternate-day schedules and from divided to single doses increases the efficacy of treatment and improves tolerability. *The minimal dose used for iron supplementation is the equivalent of 60 mg elemental iron daily.*** This dose should be used for initial empiric treatment of suspected IDA as is commonly seen in the third trimester of pregnancy and also for universal supplementation in the first trimester along with a prenatal vitamin. Doses above 100 mg daily should be administered QOD. ***Ingestion one hour before meals, on an empty stomach, with a glass of orange juice or another form of vitamin C to improve absorption, is recommended.*** Milk, calcium and antacids should not be taken at the same time as iron supplements because these interfere with absorption.

Delayed and slow-release products are not recommended due to poor absorption.

Ferrous sulfate\*\*\*: 325 mg tablet contains 65 mg elemental iron (recommended choice in pregnancy and for universal supplementation in addition to a prenatal vitamin)

Ferrous fumarate: 325 mg tablet contains 106 mg elemental iron

Ferrous gluconate: 300 mg tablet contains 34 mg of elemental iron

**Technique: IV IRON**

IV iron is associated with higher maternal hemoglobin at delivery, greater likelihood of achieving target hemoglobin and decreased adverse reactions in comparison to PO iron supplementation. Additionally, those receiving IV iron during pregnancy, had higher hemoglobin concentrations at 6 weeks postpartum with fewer gastrointestinal adverse effects.

IV iron is available in different forms. Those products which allow a high-dose schedule avoid multiple infusions and increase convenience. In addition to the prompt Hgb increase, these protocols rapidly reconstitute stores, making the advantages (single access, accelerated recovery, limited need for blood tests) outweigh the disadvantages (cost, invasiveness, risk of reactions). Slow infusion at the outset is recommended for all formulations to observe for adverse reactions. Newer regimens suggest empiric dosing of 1000 mg iron for IV replacement is appropriate.

\*\*\*Low molecular weight Iron dextran (LMW-ID, INFED): LMW-ID is the least expensive IV supplement and is given as a single infusion. A retrospective analysis of over 30 million doses of IV iron showed the large majority of serious adverse events (SAE) with ID were due to the older, HMW formulations. When these formulations are excluded, the LMW formulations (such as INFED) are safe with a SAE rate of less than 1:200,000 administrations. - ***Prepare 1000 mg in 250 cc NS. Test dose is 25 mg IV bolus over 15 minutes followed by 15 min observation for reaction.******If the test dose is well-tolerated, infuse the remainder (975 mg)******over 1 hour (range 1-4 hours).*** See **Special Considerations** below for premedication advice.

Iron sucrose (IS, VENOFER): ***Prepare 500 mg in 250 cc NS. Administer full dose over 4 hours x 2 doses given a week apart.*** Alternative dosing***:*** prepare200 mg in 100 cc NS. Administer over 30-90 min x 5 doses given QOD.

Ferric carboxymaltose: (FCM, INJECTOFER, Ferinject®): ***Prepare 750 mg in 250cc NS. Administer full dose over 15-30 min x 2 doses given a week apart.*** Delayed reactions such as muscle weakness, fatigue and bone pain due to low serum phosphate levels can occur with any IV iron but are most frequent with ferric carboxymaltose.

\*\*\*Preferred preparation in pregnancy.

**Special Considerations:**

-Failure to respond to oral iron therapy should prompt further investigation prior to prescribing IV iron replacement and may suggest an incorrect diagnosis, coexisting disease, malabsorption (sometimes caused by the use of enteric-coated tablets or concomitant use of antacids), noncompliance, or blood loss.

--Intermittent oral iron dosing has been shown to be non-inferior to daily dosing in a small randomized non-inferiority trial of third trimester pregnant people presented at the Society for Maternal-Fetal Medicine’s 2021 Virtual Annual Meeting, Jan. 25 to Jan. 30, 2021.

-If premedication is performed due to multiple drug allergies (2 or more), asthma, history of anaphylaxis, steroids are recommended prior to iron infusion including: methylprednisolone 40-125 mg IV or hydrocortisone 50-100 mg IV. In addition, acetaminophen (650 mg) can be given. Diphenhydramine use should be avoided due to vasoconstrictive effects.

-If a minor infusion reaction including myalgias, arthralgias, hand swelling, nausea, or flushing (without other hypersensitivity symptoms) occurs, stop the infusion and monitor for 15 minutes for symptom resolution. If symptoms resolve, resume the infusion at half the rate and if tolerated without symptom recurrence after 15 minutes, increase slowly to the original rate.

--After the normalization of the Hgb values, oral iron administration should be continued for at least another 4–6 months until a ferritin level of roughly 50 ng/mL has been obtained. This is especially important in the postpartum and lactating population.

**References:**

1. Anemia in Pregnancy. ACOG Practice Bulletin No.233. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021; 138 (2).e55-64..
2. California Maternal Quality Care Collaborative (CMQCC). OB hemorrhage Toolkit V3.0: Management of Iron Deficiency Anemia. July 2022.
3. C Camaschella. Iron Deficiency. Blood® 3 JANUARY 2019 | VOLUME 133, NUMBER 1.
4. Garzon, S et al. Iron Deficiency Anemia in Pregnancy: Novel Approaches for an Old Problem Oman Medical Journal [2020], Vol. 35, No. 5: e166.
5. Auerbach M and Adamson J. How We Diagnose and Treat Iron Deficiency Anemia. Am J Hematology 2016;91(1):31-39.
6. Myers B, Myers A, Moore J. Comparative efficacy and safety of intravenous ferric carboxymaltose and iron(III) hydroxide dextran in pregnancy. Obstet Med 2012;5:105–107.
7. Christoph P, Schuller C, Studer H, et al. Intravenous iron treatment in pregnancy: Comparison of high-dose ferric carboxymaltose vs. iron sucrose. J Perinat Med 2012;40:469–474.
8. Chritchley J, Dunbar Y. Adverse events associated with intravenous iron infusion (low – molecular weight iron dextran and iron sucrose): A systematic review. Transfus Altern Transfus Med 2007;9:8–36.
9. Froessler B, Collingwood J. Hodyl. Intravenous ferric carboxymaltose for anaemia pregnancy. BMC Pregnancy Childbirth 2014;14:115–119.

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