

Management of Iron Deficiency Anemia in Women

Summary

- Iron deficiency with or without anemia, has a prevalence that may exceed 30-40% and is underrecognized and undertreated.
 - Iron deficiency has a negative impact on quality of life, increased morbidity and mortality, and an association with poor fetal outcomes.
 - Its early recognition and treatment is a global issue and should be a high priority.
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Introduction

Anemia is an extremely common condition, in both developed and undeveloped countries. Data from the World Health Organization (WHO) Vitamin and Mineral Nutrition Information System for 1993-2005¹, estimated the global anemia prevalence as 24.8%, affecting 1.62 billion people. Of those affected, 41.8% occurred in pregnant women and 30.2% in nonpregnant women. This equates to 677 million pregnant women and 489 million nonpregnant women worldwide.¹ In a more recent study from the Bill and Melinda Gates Foundation of the eight causes of chronic disease affecting more than 10% of the world's population, iron deficiency anemia (IDA) affected the greatest number of people – 2.36 billion individuals worldwide.² IDA affects infants, children, adolescents and women both young and old. In pregnancy the effects of anemia are an independent risk factor for morbidity, and mortality in both the mother and fetus.³

Causes of Iron Deficiency Anemia

- **Nutritional deficiency:** Inadequate dietary iron
- **Bleeding:** This is the most common cause of iron deficiency in women from heavy menses or if postmenopausal from the gastrointestinal tract.
- **Impaired absorption:** Inflammatory bowel disease, gastric bypass surgery, celiac disease, proton pump inhibitors causing reduced gastric acid and autoimmune gastritis.
- **Pregnancy:** Pregnancy results in increased iron requirements and is common especially in women with multiple pregnancies and/or borderline iron status prior to pregnancy.

Symptoms of Iron Deficiency Anemia

- Easy fatigability, lack of stamina, decreases in exercise tolerance
- Palpitations
- Shortness of breath
- Headaches
- Cold intolerance
- Alterations in mood or depression
- Alopecia and nail changes, glossitis
- Restless legs syndrome
- Eating disturbances such as pagophagia, a form of pica, causing a pathological craving for ice. Such eating disturbances are often misrecognized leading to missed opportunities to detect anemia earlier.

Iron Deficiency Without Anemia

Some individuals with reduced or absent iron stores who have not yet developed anemia may have symptoms such as fatigue or reduced exercise tolerance. Treatment is likely to improve symptoms, and failure to treat is likely to eventually lead to anemia. The benefit in treatment has been seen in a few small trials and observational studies.^{4,5}

Consequences of Anemia

The consequences of anemia are protean irrespective of gender, or age; some of the adverse outcomes are:³

- Decreased cognitive function
- Decreased concentration and attention
- Increased incidence of preterm delivery
- Intrauterine growth retardation
- Intrauterine fetal demise
- Increased maternal and fetal infection risk

- Disturbed postpartum maternal–infant interaction
- Delayed growth and development

More worrisome is a recent report by Congdon *et al*,⁶ that studied longitudinal outcomes of long-term effects of iron deficiency at birth on the neural correlates of recognition, memory and cognition in children and concluded, not only do iron deficient neonates have delayed growth and development but a statistically significant increase in the number of cognitive and behavioral abnormalities up to ten years after iron repletion.⁶

Pregnancy

Anemia in pregnancy is a global health problem. While some degree of dilutional anemia is part of normal pregnancy physiology these changes result in mild anemia (hemoglobin 10 to 11 g/dL). Iron deficiency anemia can have serious adverse health consequences for the mother and child. Thus, it is critical to distinguish iron deficiency anemia from physiologic anemia, as well as to identify nutritional deficiencies such as Vitamin B12 and folate.

During pregnancy, physiologic changes such as hemodilution result in plasma volume expansion, estimated to be approximately 40-50% until the 30th week of gestation. In addition, a 20-30% increase in red blood cell mass is observed. This decrement in measured hemoglobin is complicated by iron deficiency at a time when there is increased maternal and fetal erythropoiesis. The preferential transfer of maternal iron to the fetus to meet red blood cell synthesis requirements, leads to further iron depletion. During delivery blood loss ranging from 250 mls to greater than 1000 mls further exacerbates the deficient state. With a blood loss at delivery of 250 mls, the total iron needed for an average pregnancy is 1,000 mg. This increases to approximately 1,375 mg with a 1,000 ml blood loss at delivery. When one considers that 30-40% of women have depleted iron stores at the beginning of pregnancy, the absolute need for iron supplementation during pregnancy becomes clear.

Postpartum

A hemoglobin level of less than 10 g/dl is seen as clinically significant postpartum anemia.⁷ This is a combination of blood-loss anemia and preexisting iron deficiency anemia. The nadir of the postpartum hemoglobin is typically reached about 48 hours after delivery. Serum ferritin cannot be used to assess iron stores since levels may be “false normal” or “false elevated” for the first few weeks after delivery. An accurate determination of residual iron stores can be assessed about 6 weeks or more after delivery, but isn’t necessary when significant anemia is present since iron deficiency may be assumed.⁶ Coexisting comorbidities such as multiparity, obesity, anemia during pregnancy, and age < 20 years, may delay recovery.^{8,9} Socioeconomic factors, especially malnutrition, have a complex interplay in the development of postpartum anemia, supported by data from the Special Supplemental Nutrition program for women, infants and children’s study. Of nearly 60, 000 participants, 27% overall, 40% of Hispanic, and 48% of African Americans were found to be anemic between 4-26 weeks postpartum, despite having normal hemoglobin levels during pregnancy.⁸

Heavy Uterine Bleeding

In premenopausal women, when menstrual blood loss exceeds 80 milliliters per cycle or lasts for more than 7 days, iron deficiency develops over time. Woman may not recognize abnormal bleeding so some helpful questions to ask include:

- How often do you change your pad or tampon?
- Does your bleeding last more than 7 days?
- Do you bleed through your clothing?
- Do you have to stay home from school or work?

Treatment

Irrespective of etiology the recognition of anemia and prompt attempts to identify and correct the problem are key to eliminating the symptoms associated with iron deficiency and decreased hemoglobin and rule out potentially dangerous causes, particularly in postmenopausal women, such as undiagnosed malignancy. Iron supplementation should be individualized with special attention given to correcting hemoglobin to normal levels and replenishing iron stores.

Oral Iron

Oral iron is the current first line standard for mild anemia down to 9.5 g/dl or so, however, 70% of those to whom it is prescribed report significant gastrointestinal perturbation markedly limiting adherence. In such cases and when more severe anemia is present or when rapid correction is required, intravenous iron is preferred. Complete replacement dosing can now be administered in 15-60 minutes. To date no serious adverse events have been reported in gravidas. In pregnant patient's intolerant of, or unresponsive to, oral iron therapy, intravenous iron should be administered to rapidly meet the body's demands without the difficult gastrointestinal toxicities of nausea, vomiting, colicky abdominal pain, diarrhea and constipation.

IV Iron

There are currently five intravenous iron formulations approved for use in the USA. Low molecular weight iron dextran, sodium ferric gluconate, iron sucrose, ferumoxytol and ferric carboxymaltose, when administered according to recommended guidelines are all safe and effective. There are currently no data on ferumoxytol use in gravidas.

Breymann *et al*, in a study of 1 gram of iron sucrose administered in five divided doses to greater than 500 women of gestational age 16 weeks and older with a diagnosis of IDA, concluded this formulation was safe and efficacious for use in pregnancy and the postpartum period, supporting existing published data.¹⁰

Ayub *et al*, studied 100 women of gestational age greater than 12 weeks with a confirmed diagnosis of IDA and concluded that complete replacement dosing in a single setting, with low molecular weight iron dextran is an effective and safe method.¹¹

This is supported in a recent publication by Auerbach *et al*, which evaluated the safety and efficacy of the rapid administration of 1 gram of low molecular weight iron dextran in 1 hour. In this study, 164 infusions in 157 pregnant women (second and third trimester), observed only four adverse reactions which resolved without

intervention. These findings were consistent with the remaining study population.¹²

All currently available intravenous iron products are probably comparable in safety and efficacy though they differ in the amount of unbound iron and in their administration protocols and elimination kinetics. Cost and convenience to the patient regarding their administration should be taken into consideration when choosing a formulation. There are limited data regarding their administration in pregnancy regardless of which formulation is chosen.

Reveiz *et al*, in the Cochrane database review of treatment of IDA in pregnancy, concluded that intravenous iron administration was superior to oral iron in achieving improvement in hemoglobin levels. Nonetheless unsubstantiated concerns about possible adverse effects such as thrombosis and allergic reactions were noted.¹³ These concerns have not been supported, however, by published data over the last 5 -7 years.

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