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Review Article

Management of postpartum iron deficiency anemia: review of literature

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ABSTRACT

Anemia is a condition in which either the number of circulating red blood cells or their hemoglobin concentration is decreased. As a result, there is decreased transport of oxygen from the lungs to peripheral tissues. The standard approach to treatment of postpartum iron deficiency anemia is oral iron supplementation, with blood transfusion reserved for more severe or symptomatic cases. There are a number of hazards of allogenic blood transfusion including transfusion of the wrong blood, infection, anaphylaxis and lung injury, any of which will be devastating for a young mother. These hazards, together with the national shortage of blood products, mean that transfusion should be viewed as a last resort in otherwise young and healthy women. Currently, there are many iron preparations available containing different types of iron salts, including ferrous sulfate, ferrous fumarate, ferrous ascorbate but common adverse drug reactions found with these preparations are mainly gastrointestinal intolerance like nausea, vomiting, constipation, diarrhoea, abdominal pain, while ferrous bis-glycinate (fully reacted chelated amino acid form of iron) rarely make complication. Two types of intravenous (IV) preparations available are IV iron sucrose and IV ferric carboxymaltose. IV iron sucrose is safe, effective and economical. Reported incidence of adverse reactions with IV iron sucrose is less as compared to older iron preparations (Iron dextran, iron sorbitol), but it requires multiple doses and prolonged infusion time. Intramuscular iron sucrose complex is particularly contraindicated because of poor absorption. It was also stated that when iron dextran is given intravenously up to 30% of patients suffer from adverse effects which include arthritis, fever, urticaria and anaphylaxis.

Keywords: Iron deficiency, Intravenous iron, Oral iron, Postpartum anemia

INTRODUCTION

Postpartum iron deficiency anemia is a major public health problem. In the United States, approximately 13% of women 0-6 months postpartum are iron deficient and 10% are anemic.¹ Low-income postpartum women in the United States are disproportionately affected by these health outcomes: 22% are anemic, 30% are iron deficient, and 10% are iron deficient and anemic

WHO report on anemia in pregnancy estimates that, 43% of non-pregnant women of reproductive age in

developing countries, and 12% in industrialized countries, are anemic; these estimates rise to 56% and 18%, respectively, by the third trimester of pregnancy.² After childbirth, Hb levels fall slightly during the first 24 hours because of blood loss and then rise over the next 2 to 5 days. Hb should return to the normal non-pregnant range by 7 days.

In Western countries, the most common cause of anemia during pregnancy and the postpartum period is iron deficiency. Daily iron demand increases nearly 10 folds from the start of pregnancy to term.³ However, less than

25% of women start their pregnancies with iron stores sufficient to meet requirements, and only 5% increase their iron intake sufficiently during pregnancy to make up that difference.³

Postpartum anemia is more common and lasts longer in poor women than in those who are better-off: between 4 and 26 weeks after giving birth, roughly one in four low-income women suffer from anemia; the proportion reaches nearly half, however, among those who were anemic during pregnancy and among black women. These findings, based on data for women enrolled in a federally sponsored nutrition program in 12 states, suggest a sharply higher prevalence of anemia among low-income women than has been found elsewhere among their better-off counterparts. They also indicate that although women's iron levels (which drop during pregnancy) typically recover 4-6 weeks after delivery, low-income women remain at risk of suffering from anemia for a substantially longer period.¹

Etiology and risk factors

The postpartum anemia risk factors supported by CDC involves three equally weighted risk markers:

- Third trimester anemia.
- Excessive blood loss during delivery.
- Multiple births.

There are three risk markers of postpartum anemia not included in the CDC criteria:

- Multiparity.
- Pre-pregnancy obesity.
- Not exclusively breastfeeding.

PATHOGENESIS OF IRON DEFICIENCY ANEMIA

Iron deficiency anemia may be classified into 3 stages: storage iron deficiency, iron deficient erythropoiesis, and iron deficiency anemia. Initially, iron body stores are preferentially utilized for accelerated erythropoiesis. After depletion of body iron stores, erythropoiesis and production of other iron-containing proteins (such as myoglobin) become limited, leading to an overt iron deficiency anemia.⁴

Anemia is exacerbated as iron-deficient erythrocytes have a shortened survival due to their fragility, which accelerates reticuloendothelial cell sequestration and destruction. The observed erythrocyte morphologic changes with the underlying iron deficiency reflect the severely hampered hemoglobin synthesis and are characterized by hypochromasia and microcytosis.⁵

Furthermore, the hemoglobin-deficient erythroid precursors are thought to undergo additional mitoses while attempting to achieve ideal cytoplasmic

hemoglobin levels, thereby exaggerating the microcytosis.⁶

DIAGNOSIS OF IRON DEFICIENCY ANEMIA

Anemia is defined as a decrease concentration of Hb in the blood, cutoff depending on age and gender, but isolated Hb measurement has both low specificity and low sensitivity. The latter can be improved by including measures of iron deficient erythropoiesis.⁷

The biomarkers of hypochromia provide information about the iron supply and are reliable markers of iron restricted erythropoiesis in complex clinical situations. An appropriate combination of laboratory tests gives evidence of iron depletion, reflects iron restricted red cells production, and so will help to establish a correct assessment of the iron status and thus the appropriate treatment.⁸

The WHO defines anemia as blood hemoglobin values of less than 7.7 mmol/l (13 g/dl) in men and 7.4 mmol/l (12 g/dl) in women. Typically, the evaluation of the cause of anemia includes a complete blood cell count, peripheral smear, reticulocyte count, and serum iron indices. The severity of anemia is based on the patient's hemoglobin/hematocrit level.⁹

Iron deficiency anemia is characterized by microcytic, hypochromic erythrocytes and low iron stores. The mean corpuscular volume is the measure of the average red blood cell volume and mean corpuscular hemoglobin concentration is the measure of the concentration of hemoglobin in a given volume of packed red blood cells.

The normal references ranges for mean corpuscular volume is 80-100fL and mean corpuscular hemoglobin concentration is 320-360g/l. The patient's cells are said to be microcytic and hypochromic, respectively, when these values are less than the normal reference range. Of note, up to 40% of patients with true iron deficiency anemia will have normocytic erythrocytes (i.e. a normal mean corpuscular volume does not rule out iron deficiency anemia).¹⁰

Iron studies diagnostic for iron deficiency anemia consist of a low hemoglobin (<7.7 mmol/l in men and 7.4 mmol/l in women), a low serum iron (<7.1 mg/l), a low serum ferritin (storage form of iron) (<30 ng/l), a low transferrin saturation (<15%), and a high total iron-binding capacity (>13.1 mmol/l).¹¹

The ferritin level may be misleading in the presence of acute or chronic inflammation as ferritin is also an acute phase reactant and thus one cannot exclude iron deficiency as the cause of anemia when the serum ferritin is normal or even elevated in the presence of an inflammatory process.¹⁰ In the presence of an underlying infection or inflammation other iron markers may be useful including the reticulocyte hemoglobin content

which, because reticulocytes are only 1-2 days old, is reflective of the iron available in the bone marrow for erythropoiesis.¹²

TREATMENT OF IRON DEFICIENCY ANEMIA

Oral iron

Iron has been used to treat anemia for more than 300 years. Oral iron therapy is the most widely prescribed treatment for iron deficiency anemia, however, there are many issues that may prevent oral iron supplementation from successfully managing iron deficiency anemia. For instance, many patients do not respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects.

Side effects may play a significant role in rates of compliance.¹³ Furthermore, the presence of bowel disease may affect the absorption of iron and thereby minimize the benefit received from oral iron therapy.¹⁴ Oral iron supplements are desirable as first-line therapy as they are safe, cheap, and effective in restoring iron balance.⁹

Side effects

The side effects of oral iron therapy include gastrointestinal disturbances characterized by colicky pain, nausea, vomiting, diarrhea, and/or constipation, and occur in about 50% of patients taking iron preparations.¹⁴ Furthermore; the most widely prescribed oral iron is mainly composed of ferrous salts.¹³

Ferrous salts are characterized by low and variable absorption rates. Its absorption can be limited by ingestion of certain foods as well as mucosal luminal damage. Therefore, ferric compounds were introduced to avoid such obstacles. However, these compounds are generally less soluble and have poor bioavailability.

Intravenous iron

Oral iron is a less than ideal treatment, however, with gastrointestinal toxicity occurring in 35% to 59% of patients, and a long course needed to resolve anemia and replenish stores.¹⁵ Non-adherence to a prescribed course of oral iron is common, and even in adherent patients, poor intestinal absorption fails to compensate for iron need in the presence of ongoing blood losses.¹⁶

While intravenous (IV) iron has the capability of bypassing all these issues, there remain concerns about the acute safety profiles of the available products and the potential for long-term harm from repeated iron administration. Although any IV iron can cause acute severe reactions, the incidence and severity of reactions are less than may be appreciated by physicians and the doses commonly administered in clinical practice are insufficient to result in parenchymal organ injury.¹⁷

Iron products

High molecular weight iron dextran

Several publications have cited safety concerns with this preparation. During a brief period in 1997, when LMW ID became unavailable, HMW ID was the only formulation available. During this period, spontaneous reports to the FDA of AEs from IV iron increased 11-fold. Numerous publications warned against the use of HMW ID.¹⁸ The National Comprehensive Cancer Network and the nursing journal of the American Society of Nephrology proscribed its use. It has been removed from the formularies of all Veterans' Administration hospitals in the United States and its protectorates and is not available in Europe. Despite this, some hospital pharmacists continue to view all iron dextran products as equals and many physicians lack awareness of the differences between the two iron dextrans.¹⁹

Mamula and associates published their experience with total dose infusion (TDI) in children with inflammatory bowel disease and reported a 9-fold increase in the incidence of AEs with HMW ID, compared with LMWID.²⁰ In a review of suspected iron dextran AEs, Fletes and colleagues noted that AEs were 8.1 times more likely to occur with HMW ID, and concluded that serious AEs related to IV iron dextran were rare and appeared to depend on the specific formulation of IV iron dextran.²¹

Low molecular weight iron dextran

Given the current state of knowledge, this is the preferred formulation of iron dextran. Unlike the iron salts, FG and IS, this formulation can be administered as an IV bolus or TDI. Eschbach and colleagues were the first to show the benefit of iron dextran in augmenting the response to erythropoietin in patients with the anemia of chronic kidney disease (CKD) undergoing dialysis.²² Subsequently, it has been shown that marked reductions in ESA dosage could be achieved with the addition of iron dextran.²³

Ferric gluconate

Following its approval for use in hemodialysis patients in 2002, FG (and later IS) rapidly replaced iron dextran as the preferred IV iron preparation. Millions of doses have been given, with AEs being almost exclusively minor infusion reactions. Although AEs have been reported with all IV irons, AEs with this formulation, when high doses are avoided, are rare.²⁴

FG administration has been shown to reduce ESA requirements in hemodialysis patients with elevated ferritin levels, to improve anemia without ESAs in iron-deficient patients with CKD and to correct anemia in dialysis patients with high serum ferritin and low transferrin saturations.^{25,26}

Iron sucrose

By far, the largest experience in the published literature is with this formulation. Aronoff and associates showed the safety of replacement and maintenance regimens of IS in hemodialysis patients.²⁷ In a randomized, controlled trial comparing IV IS to oral iron in anemic patients with non-dialysis dependent CKD, Van Wyck and colleagues showed that IS, given as 1000mg in divided doses, was more effective than oral iron.²⁸

IS can be safely administered as a 2-minute bolus or as a short infusion in doses up to 300 mg, but higher doses have been proscribed.²⁹ When higher doses are administered, even with infusions lasting 2 hours, hypotension, nausea, and low back pain are observed.

Ferric carboxymaltose

This formulation of IV iron was the first of the new agents to be approved for more rapid administration of large doses. FC can be administered as an infusion of 500-1500 mg in 15 minutes; however, only doses up to 1000 mg are currently approved. No test dose is required. Anker and colleagues published their experience with 200 mg boluses of FC in patients with left ventricular ejection fractions of 45% or less.³⁰ They concluded that treatment with IV FC in patients with chronic heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life with an acceptable side-effect profile.

Ferumoxitol

This formulation was approved by the FDA in June 2009 for iron replacement in patients with IDA and CKD. No test dose is required. This product is unique in that it can be administered as a relatively large dose (510mg, exclusive vial size) in <20 seconds. There is no data on higher doses. The published safety profile is consistent with that of LMW ID, FG, and IS.¹⁷

In a crossover study on patients with IDA and CKD not on dialysis, 510 mg of ferumoxitol or placebo was administered in 17 seconds twice in 1 week to 711 patients or placebo to 713. One significant AE (anaphylaxis) was observed in the treatment arm in a patient with a history of multiple drug allergies. The authors concluded that ferumoxitol is well tolerated and has a safety profile similar to placebo in anemic patients with CKD.³¹

Iron isomaltoside

This formulation is the newest of the three agents able to provide large doses of IV iron more rapidly than iron dextran. Iron Isomaltoside (II) is approved for administration in doses up to 20mg/kg.³²

In a cohort of 182 patients with anemia of CKD who received 584 injections given as a 100- to 200-mg bolus or TDI in doses ranging from 462 to 1800 mg in 30 to 60 minutes, no serious AEs were observed, and efficacy was consistent with established guidelines for CKD. As with FC, no test dose is required. II contains strongly bound iron that enables a controlled and slow release of bioavailable iron to iron-binding proteins with minimal free iron release.³²

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