Volume 70, Number 5
OBSTETRICAL AND GYNECOLOGICAL SURVEY

CHIEF EDITOR'S NOTE: This article is part of a series of continuing education activities in this Journal through which a total of 36 *AMA PRA Category 1 Credits*™ can be earned in 2015. Instructions for how CME credits can be earned appear on the last page of the Table of Contents.

Iron Deficiency Anemia in Women: A Practical Guide to Detection, Diagnosis, and Treatment

Arnold J. Friedman, MD,* Aryeh Shander, MD, FCCM, FCCP,† Stephanie R. Martin, DO,‡ Rebecca K. Calabrese, MD,§ Maria E. Ashton, MS, RPh, MBA,¶ Indu Lew, PharmD,‖ Melvin H. Seid, MD, FAOCG, CPI, and Lawrence Tim Goodnough, MD††**

*Chairman, Obstetrics & Gynecology, Mount Sinai Beth Israel Medical Center, and Clinical Professor of Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; †Chief of Anesthesiology, Critical Care Medicine and Hyperbaric Medicine, Englewood Hospital & Medical Center, Englewood, NJ, and Clinical Professor of Anesthesiology, Medicine and Surgery, Icahn School of Medicine at Mount Sinai, New York, NY; ‡Director, Southern Colorado Maternal Fetal Medicine, Director Maternal Fetal Medicine Services St Francis Medical Center/Centura South State, Colorado Springs, and Visiting Associate Clinical Professor, Department of Obstetrics and Gynecology, University of Colorado, School of Medicine, Aurora, CO; §Associate Chief of Medicine, Erie County Medical Center, and Assistant Professor, Department of Medicine, State University of New York at Buffalo, Buffalo, NY; ¶Clinical Pharmacist, Ashton Medica, Mason, OH; ‖Vice President, Corporate Pharmacy, Barnabas Health, South Plainfield, NJ; **Director, Clinical Research, Lyndhurst OB/GYN Associates, Winston-Salem, NC; and ††Professor of Pathology & Medicine, Stanford University, Stanford, CA

Introduction: Iron deficiency anemia (IDA) remains a widely underdiagnosed and unappreciated women's health issue, affecting women of all ages. Despite the fact that IDA is easily diagnosed and treated, it continues to be a major public health issue. The World Health Organization estimates that 30% of nonpregnant and more than 42% of pregnant women have anemia.

Methods: A multidisciplinary Group for the Research and Education on Anemia Therapy in Women (GREAT Women II) was formed, sponsored by the Society for the Advancement of Blood Management. The goal was to focus attention on the impact of IDA on women at various stages of life and evaluate and use published literature to provide a simple, evidence-based approach to diagnose and treat IDA.

Results: The group developed specific recommendations for evaluating and treating IDA in women. Initial diagnosis is defined as hemoglobin less than 12 g/dL in nonpregnant women. A trial of iron therapy (4 weeks) can be considered a first-line diagnostic tool. Alternatively, a low or normal mean corpuscular volume (<100 fL), low

Dr Friedman received honorarium from Society for the Advancement of Blood Management (SABM). Dr Shander received honorarium from SABM and consulted for Masimo, CSL, Gauss. He has been a paid advisor to the American Association of Blood Banks and the US Department of Health and Human Services. He has a financial interest in Gauss. Dr Martin received honorarium from SABM. Ms Ashton received honorarium from SABM and has consulted for American Regent. Dr Lew has been a paid speaker for Amgen and American Regent. Dr Seid received honorarium from SABM and has had grants from AMAG, Luitpold, Actavis, and Pharmacosmos. Dr Goodnough received honoraria from American Regent and Amgen.

Dr Calabrese, the spouses/life partners (if any) of all authors, and all staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations pertaining to this educational activity.

The authors has disclosed that the U.S. Food and Drug Administration has not approved the use of various parenteral iron products and erythrocyte-stimulating agents as discussed in this article. Please consult the product's labeling for approved information.

The authors are members of the multidisciplinary Group for the Research and Education on Anemia Therapy in Women (The Great Women II Project), an initiative to expand on the findings of the GREAT Women I and develop working guidelines for the detection, diagnosis, and treatment of iron deficiency anemia in women. Resources for this project were provided through the SABM with financial support from American Regent, Inc, and Luitpold Pharmaceuticals, Inc.

Correspondence requests to: Arnold J. Friedman, MD, Department of Obstetrics & Gynecology, Mount Sinai Beth Israel Medical Center, 350 E. 17th St, New York, NY 10003. E-mail: afriedma@chpnet.org.

serum ferritin (<30 μg/L), and/or low transferrin saturation (transferrin saturation <20%) is sufficient to confirm IDA. If the patient does not fit the diagnosis of IDA or fails to respond to a trial of oral iron, or mean corpuscular volume is elevated, further diagnostic evaluation is needed, including iron studies, B_{12}, folate levels, and renal function tests. If results are not definitive, and IDA persists, a hematology referral is recommended.

Conclusion: Clinicians should routinely identify and treat IDA, thereby decreasing its negative impact on health and quality of life of women.

Target Audience: Providers of primary healthcare to women.

Learning Objectives: After completing this CME activity, the learner will be better able to extend knowledge, increase awareness, and improve treatment of iron deficiency anemia in women; to summarize best practice for the detection and diagnosis of iron deficiency anemia in women; and to institute practical guidelines for the use of intravenous iron in women with iron deficiency.

The significance of iron deficiency (ID) and iron deficiency anemia (IDA) in women of reproductive age remains a widely unappreciated women's health issue. While the World Health Organization estimates that 30% of nonpregnant women and more than 42% of pregnant women suffer from anemia,[1] the misconception persists that ID and IDA are only problems in poor and developing countries. In fact, in the United States, the prevalence of ID in nonpregnant women of childbearing age is 9% to 11% and IDA 2% to 5%.[2]

Among pregnant women in the United States, the prevalence of IDA is at least 21%.[3] The reduction of ID with and without anemia among children and women of reproductive age was an objective of the US Public Health Service's Healthy People 2000 campaign[4] and remains an objective of Healthy People 2020, with a current goal of a 10% reduction in ID.[5] Despite public health initiatives, IDA continues to be underrecognized and undertreated. Safe and effective treatment options for IDA are readily available, yet underutilized, resulting in lost productivity and significant morbidity and mortality.

To help address this important health issue among women, the Society for the Advancement of Blood Management formed a multidisciplinary Group for the Research and Education on Anemia Therapy in Women (GREAT Women). The GREAT Women I project was an initiative developed to extend knowledge, increase awareness, and improve treatment of anemia in women. The GREAT Women II working group reviewed the findings from GREAT Women I and took them a step further and develop working guidelines for the detection, diagnosis, and treatment of IDA in women from adolescence through their postmenopausal years. It is primarily intended as a practical guide to the diagnosis and treatment of IDA for the health care professionals who provide primary care to women, including internists, family practitioners, and obstetrician/gynecologists.

THE BURDEN OF DISEASE

Many patients and caregivers mistakenly believe that anemia is a benign condition, unaware of IDA's significant effects on quality of life and morbidity and mortality. Women with IDA have lower vitality scores, comparable to women with serious medical conditions such as clinical depression, congestive heart failure, chronic kidney disease, and cancer. These scores improve to baseline with correction of anemia.[6–9] In childhood and adolescence, ID and IDA have been associated with decreased cognition, lower test scores in mathematics, decreased exercise tolerance, and a propensity for increased lead absorption and toxicity.[10] During pregnancy and the postpartum period, IDA is linked to premature births and low-birth-weight infants,[11] increased risk of postpartum depression,[12] poor maternal-infant interaction in the postpartum period possibly related to developmental deficits in childhood,[13,14] and increased risk of maternal transfusion and maternal mortality.[15] In the perimenopausal age group, anemia from excessive menstrual bleeding is often the indication for hysterectomy, which in turn is made more dangerous by virtue of the anemia itself. Later in adult life, IDA is associated with cognitive and physical impairment.[16] Depressed thyroid function and impaired thermoregulatory ability,[17] reduction in humoral and cell-mediated immunity,[18] and left ventricular dysfunction and cardiomyopathy have all been associated with IDA.[19] Furthermore, anemia is a potent independent multiplier of mortality in renal disease and congestive heart failure, associated with a 5 to 6 times increased relative risk in patients with both conditions.[20] A summary of the effects of IDA in women across their lifespan can be found in Table 1.

DETECTION AND DIAGNOSIS OF IRON DEFICIENCY ANEMIA

Iron deficiency anemia cannot be addressed unless it is discovered. Because effective, safe treatment options for IDA are readily available, screening for IDA in women at risk is essential for anemia detection and correction. The US Centers for Disease Control and other organizations[38,39] recommend periodic screening for anemia among high-risk populations of infants and

TABLE 1
Effects of Iron Deficiency and Anemia in Women Across Their Lifespan

	Effects of ID and Anemia
Childhood and adolescence	• Iron deficiency +/– anemia associated with developmental deficits, impaired memory, and negative effects on neurodevelopment[21,22] • IDA in children linked to lead absorption and toxicity[23–25] • ID +/– anemia linked to diminished alertness, attention span, and learning. IDA associated with diminished memory, verbal learning, and lower standardized math scores.[26] Correction of ID improves learning[27] • Quality-of-life deficits; diminished physical function, impaired work performance, depression, fatigue, loss of vitality[28]
Pregnancy and fetal development	• IDA associated with preterm delivery and lower-birth-weight newborns[28] • Decreased iron in utero may affect developmental and metabolic programming and brain development[3] • Low iron stores at birth are associated with cognitive deficits, decreased fine motor skills, and impaired language ability[29]
Postpartum	• IDA associated with palpitations, tiredness, shortness of breath, and increased incidence of infection[12] • Iron deficiency shown to cause emotional and cognitive effects including emotional instability, decreased cognition, and increased risk of postpartum depression[12]
Perimenopause	• IDA common in women with menorrhagia, occurring in as many as 20%[30] • Lower quality-of-life assessments diminished physical function; impaired work performance; caused depression, fatigue, loss of vitality, and lost work or school time; and increased clinical burden[31–34]
Postmenopause	• Quality-of-life deficits; frailty, poor cognition, diminished physical function, impaired work performance, depression, fatigue, loss of vitality[28] • More than 50% of women in nursing homes have anemia. There is an increased risk of falls in anemic nursing home residents.[35] • Anemia is a risk factor for development of dementia in the elderly.[36] • Anemia is an important comorbidity in heart disease and chronic kidney disease, doubling mortality when coupled with either. The coexistence of all three are associated with a 5–6 times relative risk.[37] Left ventricular dysfunction and cardiomyopathy have also been linked to IDA.[19]

preschool children, among pregnant women, and among specific groups of nonpregnant women of childbearing age. The American Academy of Pediatricians is more specific in recommending hemoglobin (Hb) or hematocrit measurement for all infants between 9 and 12 months of age and then 6 months later and, for children at high risk, yearly from age 2 to 5 years.[40] The American Academy of Family Physicians suggests screening infants between 6 and 12 months who are poor, black, Native American, Alaska Native, immigrants from developing countries, preterm and of low birth weight, and whose primary diet is unfortified cow's milk.[41]

Because of the high incidence of anemia in adolescent girls, the American Academy of Pediatricians recommends anemia screening for this group at all routine physical examinations.[40] The American College of Obstetricians and Gynecologists does not recommend routine screening of adolescents but does support routine screening of pregnant women at the first prenatal visit and again early in the third trimester.[42] See Table 2 for authors' screening recommendations. In addition to theabove screening guidelines, Hb or hematocrit testing should be performed based on clinical assessment. For example, any woman with heavy or frequent menstrual bleeding or uterine fibroids should be evaluated for anemia.

The initial diagnosis of anemia is relatively simple, defined by serum Hb value. The US Centers for Disease Control defines anemia in a nonpregnant woman as an Hb level of less than 12 g/dL. In pregnancy, an Hb level of less than 11 g/dL in the first and third trimester or 10.5 g/dL in the second trimester is considered anemia.[38] Although ID is by far the most common cause of anemia throughout childhood and the reproductive years, the diagnosis should be confirmed in order to provide appropriate treatment. A low mean corpuscular volume (<80) defines microcytic anemia and in the absence of hemoglobinopathy is generally sufficient to confirm the diagnosis of IDA. If the mean corpuscular volume is not confirmatory, serum ferritin and/or

TABLE 2
Recommendations for Anemia Screening in Women and Children

Population	Recommendations for Anemia Screening
Children	
Children at high risk for anemia*	Age 9–12 mo Age 18 mo Annually thereafter[38]
Women of reproductive age	
Adolescents	Screen at menarche and rescreen at least every 5 y[38]
Women anticipating pregnancy	Preconception
Pregnancy	1st Trimester—first prenatal care visit 3rd Trimester
Postpartum	Prior to hospital discharge If anemic, treat and repeat testing at 6-wk postpartum visit[43]
Perimenopause	
Perimenopause	At least every 5 y unless change in bleeding symptoms[38]
Abnormal bleeding, anatomic or clinical signs associated with anemia, eg fibroids, symptoms of anemia	Annually
Postmenopause	
Age 55–75 y	At least every 5 y, frequency based on signs or symptoms
Age >75 y	Annually

*For example, children from low-income families, those eligible for the Special Supplemental Nutrition Program for Women Infants and Children (WIC), migrant children, or recently arrived refugee children.[38]

transferrin saturation can document low iron levels and therefore IDA.[44]

Alternatively, because ID is common in women and its treatment safe and effective, a trial of iron therapy can be considered a first-line diagnostic tool. A positive response to a therapeutic trial of iron, characterized by an increase in absolute reticulocyte count at 1 week and/or Hb increase at 2 weeks, can be diagnostic of IDA.[45]

If iron therapy is effective, no further anemia workup is needed, but all IDA patients should be evaluated for a source of blood loss. In reproductive-age women, current pregnancy or a history of heavy menstrual bleeding is generally considered adequate cause, but in the absence of such history or in a postmenopausal woman, a gastroenterologic workup should be performed.[46]

If the patient does not fit the diagnosis of IDA or fails to respond to a therapeutic trial of intravenous (IV) iron, further diagnostic evaluation should be conducted, including measurements of B_{12} and folate levels as well as renal function testing.[47]

If these results are not definitive, we suggest referral to a hematologist for further diagnosis, including testing for the second most common cause of anemia, the anemia of chronic disease (ACD). Particularly in older adults and patients with chronic kidney disease, cancer, or other inflammatory conditions, ACD is often difficult to distinguish from IDA. While IDA results from an inadequate iron supply for erythropoiesis, ACD is caused by the sequestration of iron by the reticuloendothelial system most likely due to elevated levels of hepcidin, rendering it unavailable for erythropoiesis. Women with ACD usually present with increased ferritin and low or normal transferrin saturation, accompanied by elevated cytokine levels.[48]

TREATMENT OF IDA IN WOMEN

Although the treatment of IDA is fairly straightforward, it is important to have a basic understanding of iron absorption and metabolism in order to optimize therapy.[49]

Orally ingested iron comes in ferric and ferrous forms. Ferric iron must be reduced by the enzyme ferric reductase to the ferrous form before it can be absorbed by the enterocytes in the duodenum. Absorption across the cell membrane requires the action of divalent metal transporter 1 (DMT1).[50] These 2 agents are increased in ID, thereby improving iron absorption. Once inside the cell, the ferrous iron is oxidized by Fe-oxidase hephaestin back to the ferric form, which is in turn transported out of the cell into the bloodstream by the protein ferroportin, present in all iron-storing cells. Once released into plasma, ferric iron attaches to transferrin. The ferric-transferrin complex travels to the liver and spleen, where it binds to transferrin receptors on hepatocytes and macrophages, and is stored as ferritin and ultimately released by ferroportin mainly for heme synthesis in erythroblasts. The peptide hormone hepcidin inhibits the ferroportin-mediated release of ferric iron

from cells containing iron, including enterocytes in the duodenum and storage cells of the reticuloendothelial system.[51] Hepcidin is decreased in states of iron-deficient erythropoiesis and increased in iron overload and inflammatory conditions.[51] Approximately 150 mg of elemental iron is needed to increase Hb by 1 g/dL. This can be supplied either through gastrointestinal absorption or IV administration.

ORAL IRON

Oral iron, when tolerated and taken properly, is highly effective in correcting IDA. Natural dietary heme-iron sources such as red meat are best absorbed and tolerated, but most oral treatment is provided through supplements. These are safe, cheap, and effective sources of iron replacement.[52] Oral iron comes in ferric and ferrous forms. Ferrous iron is preferred because it is better absorbed from the intestinal tract.[53] The 3 most common oral iron preparations are ferrous sulfate, ferrous gluconate, and ferrous fumarate. Dosing is based on the amount of elemental iron in each pill (sulfate 65 mg, gluconate 35 mg, and fumarate 108 mg).[53] See Table 3 for relative potency and dosing. Because higher doses are less well absorbed from the duodenum, the total daily dose should be divided into 2 to 4 fractions, each taken on an empty stomach (1 hour before eating or 2 hours after). Maintenance of stomach acidity is important for absorption, and vitamin C (ascorbic acid) with each dose may be beneficial. The recommended daily dose of oral iron for the treatment of IDA is 150 to180 mg/d of elemental iron in divided doses 2 to 3 times per day.[38] A positive response is confirmed by reticulocytosis, generally seen within 1 week, and increased Hb levels approximately 2 to 3 weeks after iron supplementation is started.[52,54]

The major problem with oral iron supplements is that at least 20% and as many as 40% of patients cannot tolerate them because of gastrointestinal adverse effects, including abdominal distress, nausea, vomiting, constipation, or diarrhea.[55–57] It is important for prescribers to inform patients of these potential adverse effects prior to commencing oral iron therapy and to encourage an open dialogue so that should negative effects occur, alternative therapies can be provided.

In addition to the problem of adverse effects, impaired iron absorption also can be an issue. Inflammatory bowel disease and other malabsorption states, prior gastric bypass surgery, and concomitant administration of drugs can inhibit iron absorption.[58–60] The common practice of administering iron supplements with food in an attempt to alleviate gastrointestinal adverse effects can effectively decrease absorption by 40% to 66%.[55] Oral iron agents need to rapidly dissolve in the stomach in order to be absorbed in the duodenum or upper jejunum. Long-acting or enteric-coated formulations designed to increase compliance and limit adverse effects may actually be ineffective, because they do not dissolve in the stomach.[61]

INTRAVENOUS IRON

Traditionally, IV iron has been reserved for IDA patients in whom oral iron is not tolerated or ineffective or for situations in which time is of the essence such as late pregnancy or severe anemia, or when another bleeding episode is imminent as with heavy menstrual cycles or dysfunctional uterine bleeding. Intravenous administration bypasses the absorption difficulties associated with oral iron, and numerous clinical studies show a greater rise in Hb concentration and iron stores over a shorter period using IV iron when compared with oral iron.[62–68] In addition, IV iron may be useful in the treatment of ACD. High single doses of IV iron may overcome the block caused by hepcidin in patients with this condition.[69,70]

Prior to 1999, iron dextran was the only IV iron product available in the United States. However, reports of

TABLE 3
Common Oral Iron Supplements[52]

Iron Supplement	Common Brand Names	Elemental Iron
Ferrous sulfate	Feosol, Slow-Fe, Fer-in-Sol	65 mg
Ferrous gluconate	Fergon, Floradix	35 mg
Ferrous fumarate	FerroSequels, Nephro-Fer	108 mg
Carbonyl iron	Feosol with Carbonyl Iron, Ferra-Cap, Icar, Ircon	45 mg
Ferrous bisglycinate	Comfort Iron	25 mg
Polysaccharide iron complex	Niferex,	50 mg
	Niferex-150	150 mg
	Ferrex-150	
Heme iron polypeptide	Proferrin ES, Proferrin Forte	12 mg

Iron preparations vary in elemental iron content. Recommended IDA therapy is 150 to 180 mg/d divided into 2 to 3 doses.

TABLE 4
Intravenous Iron Comparison Chart

	Iron Dextran[78,79]	Iron Sucrose[80]	Ferric Gluconate[81]	Ferumoxytol[82]	Ferric Carboxymaltose[83]
Trade name(s)	DexFerrum (American Regent Inc) InFeD (Watson Pharma)	Venofer (American Regent Inc)	Ferrlecit (Sanofi Aventis US) Generic (Watson Pharma)	Feraheme (AMAG Pharmaceuticals)	Injectafer (American Regent Inc)
Indication	Iron deficiency in patients whom oral administration is unsatisfactory or impossible	Iron deficiency anemia in adult and pediatric patients with chronic kidney disease (CKD)	Iron deficiency anemia in adult and pediatric patients with CKD receiving hemodialysis who are receiving supplemental erythropoietin therapy	Iron deficiency anemia in adult patients with CKD	Iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron or who have non–dialysis-dependent CKD
Black-box warning	Yes	No	No	No	No
Route of administration	IV injection IV infusion (not FDA approved) IM injection (InFed only)	IV injection IV infusion	IV injection IV infusion	IV injection IV infusion	IV injection IV infusion
Maximum FDA-approved single dose	100 mg	400 mg	125 mg	510 mg	750 mg
Pediatric indication	Yes >4 mo of age Based on weight	Yes >2 y of age	Yes >6 y of age	No	No
Pregnancy category	Category C	Category B	Category B	Category C	Category C
Lactating women	Traces of unmetabolized iron dextran are excreted in human milk.	It is not known whether iron sucrose is excreted in human milk.	It is not known whether ferric gluconate is excreted in human milk. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant	It is not known whether ferumoxytol is present in human milk.	Mean breast milk iron levels were higher in lactating women receiving ferric carboxymaltose than in lactating women receiving oral ferrous sulfate.

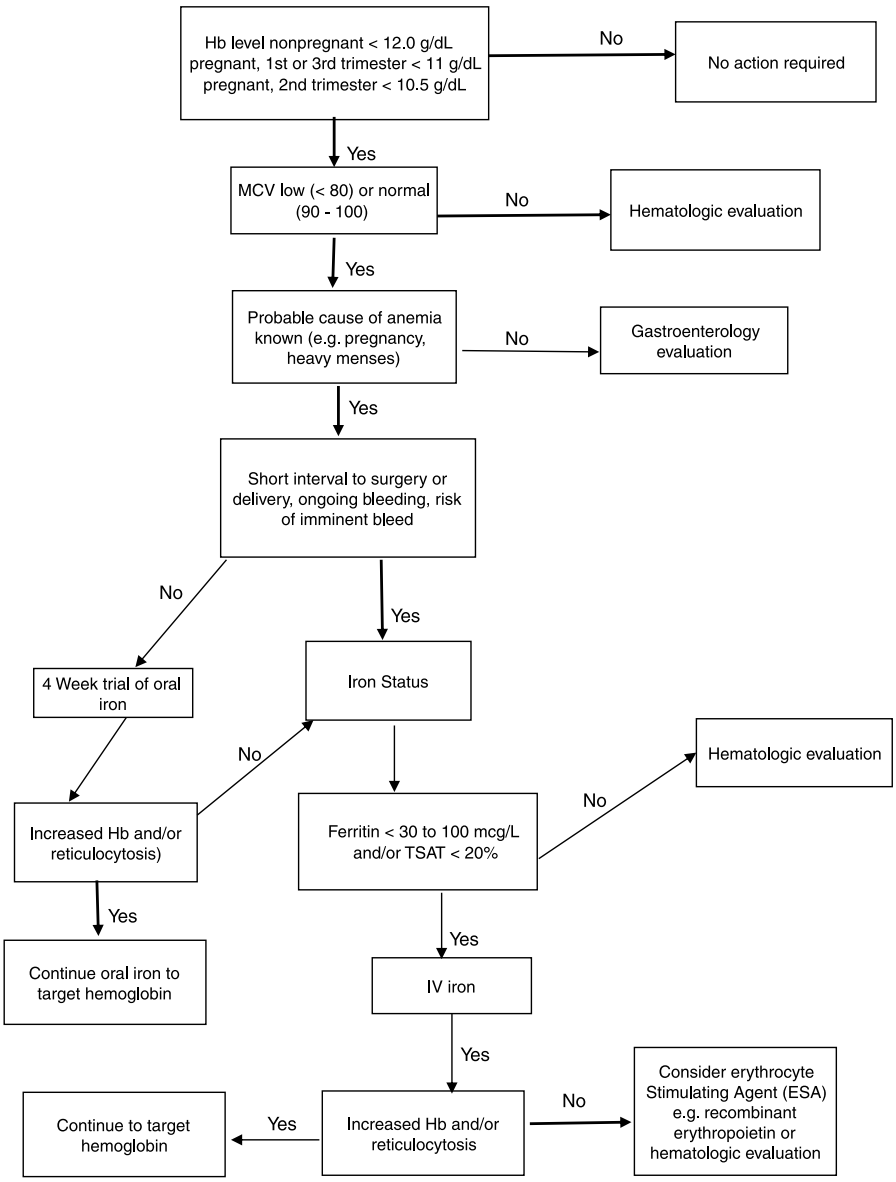

FIG. 1. Recommendations for IDA evaluation and treatment of women of reproductive age.

adverse events limited its use. Such events were reported in approximately 26% of patients. Most of these reactions were mild and self-limited, but reportedly 3% of patients experienced severe reactions (hives, swelling, convulsions), and 0.6% suffered life-threatening anaphylaxis.[71] Other studies suggest the risk is far lower and related to the particular type of iron dextran used, with the high-molecular-weight formulation having more reactions than the low-molecular-weight version. Both carry a black-box warning from the US Food and Drug Administration (FDA) and require a test dose prior to initiating treatment.[72]

Unfortunately, the occurrence of anaphylactic reactions to iron dextran has led to the common misconception that IV iron preparations are high-risk agents. In 1999, sodium ferric gluconate (Ferrlecit) was approved for use in the United States followed in 2000 by the approval of iron sucrose (Venofer), both without significant risk of these severe anaphylactic reactions and no requirement for a test dose. Iron sucrose and ferric gluconate rapidly replaced iron dextran as the IV iron agents of choice in patients with chronic kidney disease. Several retrospective studies demonstrate a lower incidence of serious acute events with these products compared with iron dextran and have allowed successful treatment in patients sensitive to iron dextran.[73–76]

Currently, including the 2 iron dextrans, there are 6 IV iron formulations available in the United States:

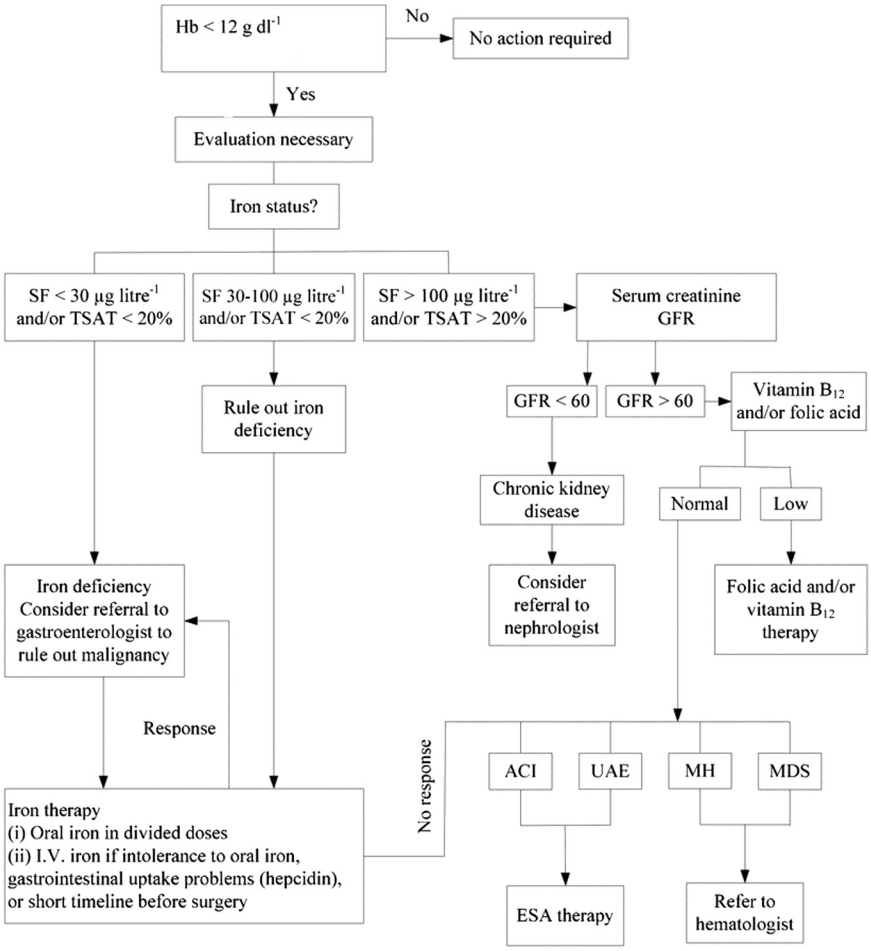

FIG. 2. Recommendations for IDA evaluation and treatment of postmenopausal women. Figure adapted from Goodnough and Schrier.[88] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work (John Wiley & Sons, Inc., NJ) and from the owner of copyright in the translation or adaptation.

low-molecular-weight iron dextran (INFeD), high-molecular-weight iron dextran (Dexferrum), sodium ferric gluconate complex in sucrose, iron sucrose, ferumoxytol (Feraheme), and ferric carboxymaltose (Injectafer). The advantages of the nondextran IV iron preparations are that they have an extremely low risk of anaphylaxis or other serious adverse effects, do not require a test dose, and can be given as an IV push over a few minutes. However, the dextran formulations maintain the advantage that they can be delivered as a total dose infusion over a few hours (unlabeled indication), whereas all the newer agents are limited by an approved maximum dose requiring multiple doses to reach the total requirement in many cases. Two of the newer formulations provide a reasonable compromise. Ferric carboxymaltose (maximum dose, 750 mg) and ferrumoxytol (maximum dose, 510 mg) can be administered by IV push in only 2 or 3 doses to reach the total requirement, respectively.[77]

The ability to administer fewer, higher doses is much more convenient and potentially more cost-effective for both the patient and the caregiver, especially in the obstetrics and gynecology population, where the vast majority of patients requiring iron replacement are either awaiting discharge after childbirth or being treated on a strictly outpatient basis. The reduced number of administrations needed to deliver the required total dose may increase adherence to therapy, increasing both the

The cumulative dose required for hemoglobin (Hb) restoration and repletion of iron stores is calculated by the following:

Cumulative iron deficit (mg) = body wt (kg) x [target Hb (g/dL) – actual Hb (g/dL)] x 2.4 + iron storage depot (mg)*

Example: A woman weighing 65 kg with an Hb level of 9 g/dL would have a body iron deficit of about 1280 mg.

[65kg X (14-9) g/dL x 2.4] + 500mg = 1280mg

*Depot iron for body weight 35 kg and above = 500 mg

FIG. 3. Iron deficit/iron dose calculation.[90]

success and speed of repletion. The properties, indications, and dosing of each parental iron compound are presented in Table 4.

Despite the standard approach of using oral iron as first-line therapy for IDA, the growing evidence for the greater efficacy of IV preparations along with their safety has convinced many experts that IV iron is frequently the preferred treatment. Intravenous iron may be particularly suitable for the treatment of IDA in pregnant women.[67,84] Studies of IV iron use in pregnancy and in the postpartum period indicate that these patients may require as much as 1600 mg of iron. Furthermore, pregnant women tend to become more anemic as pregnancy progresses, leaving less time to correct it prior to delivery. Reveiz et al[85] conducted a systematic Cochrane database review of the medical literature on the treatment of IDA in pregnancy and concluded that the administration of IV iron was superior to the use of oral iron supplementation in improving Hb levels, although they could not find a proven benefit in clinical outcome. These factors support the use of IV iron as the treatment of choice for specific situations in pregnancy but do not yet allow us to recommend this treatment modality for all anemic pregnancies.

In women with excessive uterine bleeding, supplemental oral iron therapy is often insufficient to keep pace with ongoing iron losses associated with recurring menses. Intravenous iron therapy has been compared with oral iron in at least 2 studies of women with heavy menstrual bleeding and IDA. Both of these studies confirmed IV iron's superior efficacy compared with oral iron, with significantly more women reaching target Hb levels and greater Hb increases.[86,87] In addition to greater increases in Hb, Kim and colleagues[86] found highly significant improvements in serum ferritin levels in women receiving their total repletion dose in 200-mg (iron sucrose) IV increments 3 times a week compared with very small increases in women treated with oral iron (170.1 vs 4.1 μg/L; $P < 0.0001$), indicating an advantage for improving iron stores. In another study by van Wyck et al,[68] patients treated with 1000 mg or more ferric carboxymaltose reported not only greater Hb gains, but also increases in vitality, physical function, and improvements in symptoms of fatigue. Algorithms for the detection and treatment of IDA in women of reproductive age and postmenopausal women can be found in Figures 1 and 2.

If IV iron fails to produce the desired Hb increase, if there is a time pressure as with pregnancy near term or severe anemia, or if the diagnosis is ACD, the addition of an erythropoietic-stimulating agent (ESA) such as recombinant erythropoietin is generally effective, although this may be an off-label use of the drug. This has been shown even after iron alone has failed. Use of ESA has been shown to shorten the response time compared with iron alone both in pregnant and nonpregnant women.[89,90] The clinician should be aware that ESAs carry an FDA black-box warning regarding the potential risk of thromboembolic phenomena, particularly in cancer patients with Hb target levels of greater than 11 g/dL.

CALCULATION OF IRON DOSE

The patient's iron deficit and the required dose of iron can be calculated using the Ganzoni formula, which is applicable across many indications. The Ganzoni formula uses body weight, target and actual Hb level, and iron stores to estimate the amount of iron required by the patient. This formula is commonly used to determine the dose of IV iron replacement (Fig. 3).[91]

REIMBURSEMENT

Ensuring appropriate insurance reimbursement for the administration of IV iron to patients with IDA requires an understanding of the indications for and

appropriate use of the individual iron preparations as well as the mechanisms for obtaining authorization to use them. The current environment of commercial payers, government programs, and accountable care organizations, with evolving changes in payment policies, coupled with multiple treatment options for patients with IDA, can make navigating the reimbursement process somewhat challenging. Although these products have been widely used to treat anemia and are very similar in function, each formulation has its own highly specific indications. Only iron dextran and ferric carboxymaltose have the FDA-approved indication for treatment of uncomplicated IDA, but still require previous failure or intolerance of prior oral iron therapy. Generally, IV iron is covered by Medicare, Medicaid, and private payers when the product is used according to its FDA-approved indications, and the treatment is deemed medically necessary. However, reimbursement policies vary for different insurance carriers, different states, or even by individual plans. For example, Aetna's policy for IV iron therapy[91] considers IV iron therapy medically necessary in patients unable to tolerate or comply with oral iron or who are losing blood at a rate too rapid for oral intake to compensate for the loss. Iron deficiency anemia due to heavy uterine bleeding is considered to be an indication in which IV iron therapy is deemed medically necessary. However, they consider the use of IV iron in anemia of pregnancy "experimental" unless the patient meets the previously mentioned criteria.[90]

CONCLUSIONS

Iron deficiency anemia affects women of all ages, with potentially serious and long-lasting consequences. Iron deficiency anemia is readily diagnosable and easily treated, yet it continues to be a public health issue, even in affluent nations like the United States. The goal of this review was to focus the clinician's attention on the impact of IDA on women at various stages of life and provide a simple, evidence-based approach to its identification and treatment. We hope to encourage health care providers to look for IDA and correct it when encountered, thereby decreasing its negative impact on health and quality of life of women.

REFERENCES

1. McLean E, Cogswell M, Egli I, et al. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. *Public Health Nutr*. 2009;12:444–454.
2. Looker AC, Dallman PR, Carroll MD, et al. Prevalence of iron deficiency in the United States. *JAMA*. 1997;277:973–976.
3. Cao C, O'Brien K Pregnancy and iron homeostasis: an update. *Nutr Rev*. 2013;71:35–51.
4. Public Health Service. *Healthy People 2000, National Health Promotion and Disease Prevention Objectives*. Washington, DC: US Department of Health and Human Services, Public Health Service; 1991. DHHS Publication no (PHS) 91-50212.
5. US Department of Health and Human Services. Office of Disease Prevention and Health Promotion. Healthy People 2020. Washington, DC. Available at: http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=29. Accessed April 8, 2014.
6. Ando K, Morita S, Higashi T, et al. Health-related quality of life among Japanese women with iron-deficiency anemia. *Qual Life Res*. 2006;15:1559–1563.
7. Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute–CKD study. *Am J Kidney Dis*. 2005;45:658–666.
8. Jones M, Schenkel B, Just J, et al. Epoetin alfa improves quality of life in patients with cancer: results of meta-analysis. *Cancer*. 2004;101:1720–1732.
9. Hahn EA, Cella D, Chassany O, et al. Precision of health-related quality-of-life data compared with other clinical measures. *Mayo Clin Proc*. 2007;82:1244–1254.
10. Pollack S, George JN, Reba R, et al. The absorption of nonferrous metals in iron deficiency. *J Clin Invest*. 1965;44:1470–1473.
11. Levy A, Fraser D, Katz M, et al. Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. *Eur J Obstet Gynecol Rep Biol*. 2005;122:182–186.
12. Milman N. Postpartum anemia I: definition, prevalence, causes, and consequences. *Ann Hematol*. 2011;90:1247–1253.
13. Perez EM, Hendricks MK, Beard JL, et al. Mother-infant interactions and infant development are altered by maternal iron deficiency anemia. *J Nutr*. 2005;135:850–855.
14. Beard JL, Hendricks MK, Perez EM, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. *J Nutr*. 2005;135:267–272.
15. Brabin BJ, Hakimi M, Pelletier D. An analysis of anemia and pregnancy-related maternal mortality. *J Nutr*. 2001;131:604S–614S.
16. Petranovic D, Batinac T, Petranovic D, et al. Iron deficiency anaemia influences cognitive functions. *Med Hypotheses*. 2008;70:70–72.
17. Beard JL, Borel MJ, Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anemia. *Am J Clin Nutr*. 1990;52:813–819.
18. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. *J Nutr*. 2001;131:S568–S580.
19. Metivier F, Marchais SJ, Guerin A, et al. Pathophysiology of anaemia: focus on the heart and blood vessels. *Nephrol Dial Transplant*. 2000;15(suppl 3): 14–18.
20. Herzog C. Presented at the 6th Annual Scientific Meeting of the Heart Failure Society of America; September 22–25, 2002, Boca Raton, FL. Abstract 226.
21. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. *Arch Pediatr Adolesc Med*. 2006;160:1108–1113.
22. Bruner AB, Joffe A, Duggan AK, et al. Randomized study of cognitive effects of iron supplementation in nonanemic iron-deficient adolescent girls. *Lancet*. 1996;348:992–996.
23. Six KM, Goyer RA. The influence of iron deficiency on tissue content and toxicity of ingested lead in rats. *J Lab Clin Med*. 1972;79:128–136.
24. Barton JC, Conrad ME, Nuby S, et al. Effects of iron in the absorption and retention of lead. *J Lab Clin Med*. 1978;92:536–547.
25. Watson WS, Morrison J, Bethel MI, et al. Food iron and lead absorption in humans. *Am J Clin Nutr*. 1986;44:248–256.
26. Zlotkin S. Clinical nutrition: 8. The role of nutrition in the prevention of iron deficiency anemia in infants, children and adolescents. *CMAJ*. 2003;168:59–63.
27. Alton I. Iron deficiency anemia. In: Stang M, Story M, eds. *Guidelines for Adolescent Nutrition Services*. Minneapolis, MN: Center

for Leadership, Education and Training in Maternal and Child Nutrition, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota; 2005:101–108.
28. Friedman A, Chen Z, Ford P, et al. Iron deficiency anemia in women across the life span. *J Womens Health*. 2012;21:1282–1289.
29. Tamura T, Goldenberg RL, Hou J, et al. Cord serum ferritin concentrations and mental and psychomotor development of children at 5 years of age. *J Pediatr*. 2002;140:165–170.
30. Vercellini P, Vendola N, Ragni G, et al. Abnormal uterine bleeding associated with iron-deficiency anemia. *J Reprod Med*. 1993;38:502–504.
31. Shankar M, Chi C, Kadir RA. Review of quality of life: menorrhagia in women with or without inherited bleeding disorders. *Haemophilia*. 2008;14:15–20.
32. Côté I, Jacobs P, Cumming DC. Work loss associated with increased menstrual loss in the United States. *Obstet Gynecol*. 2002;100:683–687.
33. Côté I, Jacobs P, Cumming DC. Use of health services associated with increased menstrual loss in the United States. *Am J Obstet Gynecol*. 2003;188:343–348.
34. Cs Philipp Faiz A, Dowling n, et al. Age and prevalence of bleeding disorders in women with menorrhagia. *Obstet Gynecol*. 2005;105:61–66.
35. Pandya N, Bookhart B, Mody SH, et al. Study of anemia in long-term care (SALT): prevalence of anemia and its relationship with the risk of falls in nursing home residents. *Curr Med Res Opin*. 2008;24:2139–2149.
36. Hong C, Falvey C, Harris T. Anemia and risk for dementia in older adults: findings from the Health ABC study. *Neurology*. 2013;81:528–533.
37. Herzog CA, Muster HA, Li S, et al. Impact of congestive heart failure, chronic kidney disease, and anemia on survival in the Medicare population. *J Card Fail*. 2004;10:467–472.
38. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Morb Mortal Wkly Rep*. 1998;47:1–36.
39. Evidence Syntheses, No. 40. *Oregon Evidence-Based Practice Center*. Rockville, MD: Agency for Healthcare Research and Quality; 2006.
40. Simon GR, Baker C, Barden GA, et al.; Committee on Practice and Ambulatory Medicine. Bright Futures Periodicity Schedule Workgroup. 2014 Recommendations for pediatric preventive health care. *Pediatrics*. 2014;133:568–570.
41. American Academy of Family Physicians. *Age Charts for Periodic Health Examination*. Kansas City, MO: American Academy of Family Physicians; 1994. Reprint no. 510.
42. ACOG Practice Bulletin No 95. Anemia in pregnancy. *Obstet Gynecol*. 2008;112:201.
43. Bergmann RL, Richter R, Bergmann KF, et al. Prevalence and risk of early postpartum anemia. *Eur J Obstet Gynecol Reprod Biol*. 2010;150:126–131.
44. Guyatt GH, Oxman AD, Ali M. Laboratory diagnosis of iron deficiency anemia. *J Gen Intern Med*. 1992;7:145–153.
45. British Committee for Standards in Haematology. UK guidelines on the management of iron deficiency in pregnancy. Available at: http://www.bcshguidelines.com/documents/UK_Guidelines_iron_deficiency y_in_pregnancy.pdf. Accessed September 3, 2013.
46. Zhu A, Kaneshiro M, Kaunitz JD. Evaluation and treatment of iron deficiency anemia: a gastroenterological perspective. *Dig Dis Sci*. 2010;55:548–559.
47. Goodnough LT, Mathias A, Earnshaw P, et al. Detection, evaluation, and management of perioperative anemia in the elective orthopedic surgery patient. NATA Guidelines. *Br J Anaesth*. 2011;106:13–22.
48. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352:1011–1023.
49. Shander A, Cappellini MD, Goodnough LT. Iron overload and toxicity: the hidden risk of multiple blood transfusions. *Vox Sang*. 2009;97:185–197.
50. Morgan EH, Oates PS. Mechanisms and regulation of intestinal iron absorption. *Blood Cells Mol Dis*. 2002;29:384–399.
51. Ganz T. Hepcidin and iron regulation, 10 years later. *Blood*. 2011;117:4425–4433.
52. Johnson-Wimbly T, Graham D. Diagnosis and management of iron deficiency anemia in the 21st century. *Ther Adv Gastroenterol*. 2011;4:177–184.
53. Santiago P. Ferrous versus ferric iron formulations for the treatment of iron deficiency: a clinical overview. *Sci World J*. 2012;2012:846824.
54. National Institutes of Health (NIH) Dietary supplement fact sheet; iron. Bethesda, MD. Available at: http://ods.od.nih.gov/factsheets/Iron-HealthProfessional/. Accessed September 5, 2013.
55. Arcangelo V, Peterson A. Chapter 55. Anemias (Kelly Barranger). *Pharmacotherapeutics for Advanced Practice A Practical Approach*. 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2006:800.
56. Charytan C, Qunibi W, Bailie GR. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron Clin Pract*. 2005;100:c55–c62.
57. Al-Momen AK, Al-Meshari A, Al-Nuaim L, et al. Intravenous iron sucrose complex in the treatment of iron deficiency and anemia during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 1996;69:121–124.
58. Macdougall IC. Strategies for iron supplementation: oral versus intravenous. *Kidney Int Suppl*. 1999;69:S61–S66.
59. van Wyck DB, Roppolo M, Martinez CO, et al. for the United States Iron Sucrose (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int*. 2005;68:2846–2856.
60. Agarwal R, Rizkala AR, Bastani B, et al. A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. *Am J Nephrol*. 2006;26:445–454.
61. Little DR. Ambulatory management of common forms of anemia. *Am Fam Physician*. 1999;59:1598–1604.
62. Qunibi WY, Martinez C, Smith M, et al. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis dependent chronic kidney disease patients. *Nephrol Dial Transplant*. 2011;26:1599–1607.
63. Li H, Wang SX. Intravenous iron sucrose in peritoneal dialysis patients with renal anemia. *Perit Dial Int*. 2008;28:149–154.
64. Spinowitz BS, Kausz AT, Baptista J, et al. Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol*. 2008;19:1599–1605.
65. Besarab A, Amin N, Ahsan M, et al. Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *J Am Soc Nephrol*. 2000;11:530–538.
66. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel disease. *Inflamm Bowel Dis*. 2007;13:1545–1553.
67. Breymann C. The use of iron sucrose complex for anemia in pregnancy and the postpartum period. *Semin Hematol*. 2006;43 (suppl 6): S28–S31.
68. van Wyck DB, Mangione A, Morrison J, et al. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. *Transfusion*. 2009;49:2719–2728.
69. Nemeth E, Ganz T. The role of hepcidin in iron metabolism. *Acta Hematol*. 2009;122:78–86.
70. Auerbach M, Coyne D, Ballard H. Intravenous iron: from anathema to standard of care. *Am J Hematol*. 2008;83:580–588.
71. Aronoff GM, Bennett WM, Blumenthal S, et al. Iron sucrose in hemodialyisis patients: safety and efficacy of iron replacement and maintenance therapy. *Kidney Int*. 2004;66:1193–1198.
72. Chertow GM, Mason PD, Vaage-Nilsen O, et al. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant*. 2006;21:378–382.
73. Michael B, Coyne DW, Fishbane S, et al. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. *Kidney Int*. 2002;61:1830–1839.

74. Coyne DW, Adkinson NF, Nissenson AR, et al. Sodium ferric gluconate complex in hemodialysis patients. II. Adverse reactions in iron dextran-sensitive and dextran-tolerant patients. *Kidney Int*. 2003;63:217–224.
75. Bailie GR. Comparison of rates of reported adverse events associated with I.V. iron products in the United States. *Am J Health Syst Pharm*. 2012;69:310–320.
76. Charytan C, Schwenk MH, Al-Saloum MM, et al. Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract*. 2004;96:c63–c66.
77. Peebles G, Stanley S. Evaluation of service reconfiguration for managing intravenous iron supplementation in non-hemodialysis patients with chronic renal failure. *J Outcomes Res*. 2004;8:15–25.
78. *InFeD* [package insert]. Morristown, NJ: Watson Pharma, Inc; 2009.
79. *Dexferrum* [package insert]. Shirley, NY: American Regent, Inc; 2008.
80. *Venofer* [package insert]. Shirley, NY: American Regent, Inc; 2011.
81. *Ferrlecit* [package insert]. Bridgewater, NJ: Sanofi Aventis, Inc; 2011.
82. *Feraheme* [package insert]. Lexington, MA: AMAG Pharmaceuticals, Inc; 2009.
83. *Injectafer* [package insert]. Shirley, NY: American Regent, Inc; 2013.
84. Qunibi W, Dinh Q, Benjamin J Safety and tolerability profile of ferric carboxymaltose (FCM) a new high dose intravenous iron, across ten multi-center trials. *J Am Soc Nephrol*. 2007;18:SU-PO1029.
85. Reveiz L, Gyte GM, Cuervo LG, et al. Treatments for iron-deficiency anemia in pregnancy. *Cochrane Database Syst Rev*. 2011: CD003094.
86. Kim YH, Chung HH, Kang SB, et al. Safety and usefulness of intravenous iron sucrose in the management of preoperative anemia in patients with menorrhagia: a phase IV, open label, prospective, randomized study. *Acta Haematol*. 2009;121:37–41.
87. Breymann C, Visca E, Huch R, et al. Efficacy and safety of intravenously administered iron sucrose with and without adjuvant recombinant human erythropoietin for the treatment of resistant iron-deficiency anemia during pregnancy. *Am J Obstet Gynecol*. 2001;184:662–667.
88. Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly. *Am J Hematol*. 2014;89:88–96.
89. Breymann C, Richter C, Huttner C, et al. Effectiveness of recombinant erythropoietin and iron sucrose vs. iron therapy only, in patients with postpartum anaemia and blunted erythropoiesis. *Eur J Clin Invest*. 2000;30:154–161.
90. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. *Schweiz Med Wochenschr*. 1970;100:301–303.
91. Aetna Clinical Policy Bulletin: intravenous iron therapy Available at: http://www.aetna.com/cpb/medical/data/500_599/0575.html. Accessed September 21, 2013.