

Iron deficiency anemia in women: pathophysiological, diagnosis, and practical management

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EPIDEMIOLOGY AND ETIOLOGY OF ANEMIA

Anemia remains a significant global health issue, especially among children and women, regardless of socioeconomic status or geographic location. According to the World Health Organization (WHO), iron deficiency and iron deficiency anemia (ID/IDA) in the general population are the most debilitating nutritional deficiencies worldwide in the 21st century, with women being at particularly high risk^{1,2}. Among 1.6 million people analyzed from 93 countries in the period between 1993 and 2005, the estimated worldwide prevalence of anemia (defined as an hemoglobin (Hb) <13 g/dL for males, <12 g/dL for nonpregnant females, and <11 g/dL for pregnant women and children) was 47.5% in children of preschool age, 25.4% in children of school age, 30.2% in nonpregnant women, and 41.8% in pregnant women^{1,2}. In Brazil, the prevalence of anemia was moderate (20–39.9%) and severe ($\geq 40\%$) for pregnant women and preschoolers, respectively^{1,3}. ID accounts for more than 60% of anemia cases (approximately 27% of the world's population)^{1,2}.

ID in women has substantial health consequences with subsequent socioeconomic hazards, including impaired educational performance, decreased work capacity and productivity, and poor pregnancy outcomes. In 2017, the Global Burden of Diseases Study reported that dietary ID remains the fourth leading cause of years lived with disability in women^{1,4}.

ABSOLUTE IRON DEFICIENCY VERSUS FUNCTIONAL IRON DEFICIENCY

Iron plays a key role in many physiological processes, including energy production, oxygen transport by Hb in red blood cells (RBCs), DNA synthesis and oxidation-reduction reactions,

myocyte function, and cell division. To meet but not exceed daily iron requirements for erythrocyte production and cellular metabolism (25 mg/day), iron is absorbed via the diet (1–2 mg/day) and salvaged from erythrocyte breakdown by macrophages (20–25 mg/day); any remaining iron requirements are met through the body's residual iron stores (a total of 3–5 g in adults)⁵. Daily iron loss (~1–2 mg/day) cannot be regulated, and thus, tight hemostatic controls exist to regulate iron absorption, recycling, and storage⁵ (Figure 1).

Total body iron is distributed among Hb within erythroid precursors and mature RBCs (it represents more than two-thirds of the body's iron), myoglobin in muscles, iron-dependent proteins for cellular metabolism, and storage iron (predominantly in the liver, spleen, and bone marrow). A minority of the body's total iron is found in the circulation, where it is bound to transferrin. Iron absorption and tissue iron availability are closely regulated by hepcidin, a protein produced predominantly by hepatocytes, and it exerts control over systemic iron homeostasis by degrading ferroportin. Ferroportin is the key iron exporter expressed on macrophages and duodenal enterocytes that allows the recycling of iron from broken down/senescent erythrocytes into plasma and the absorption of iron from the gut into circulation, respectively. Hepcidin expression is increased by high body iron levels and inflammation and decreased by erythropoiesis, hypoxia, and ID⁶.

In an absolute ID state, total body iron stores are reduced. Suppressed hepcidin levels lead to reduced ferroportin degradation, which in turn facilitates the absorption of iron from the gut (with help from divalent meta-transporter 1 [DMT1]) and allows iron export from macrophages and hepatocytes into the circulation. DMT1 and ferroportin are also upregulated by hypoxia-inducible factor 2a, which further facilitates

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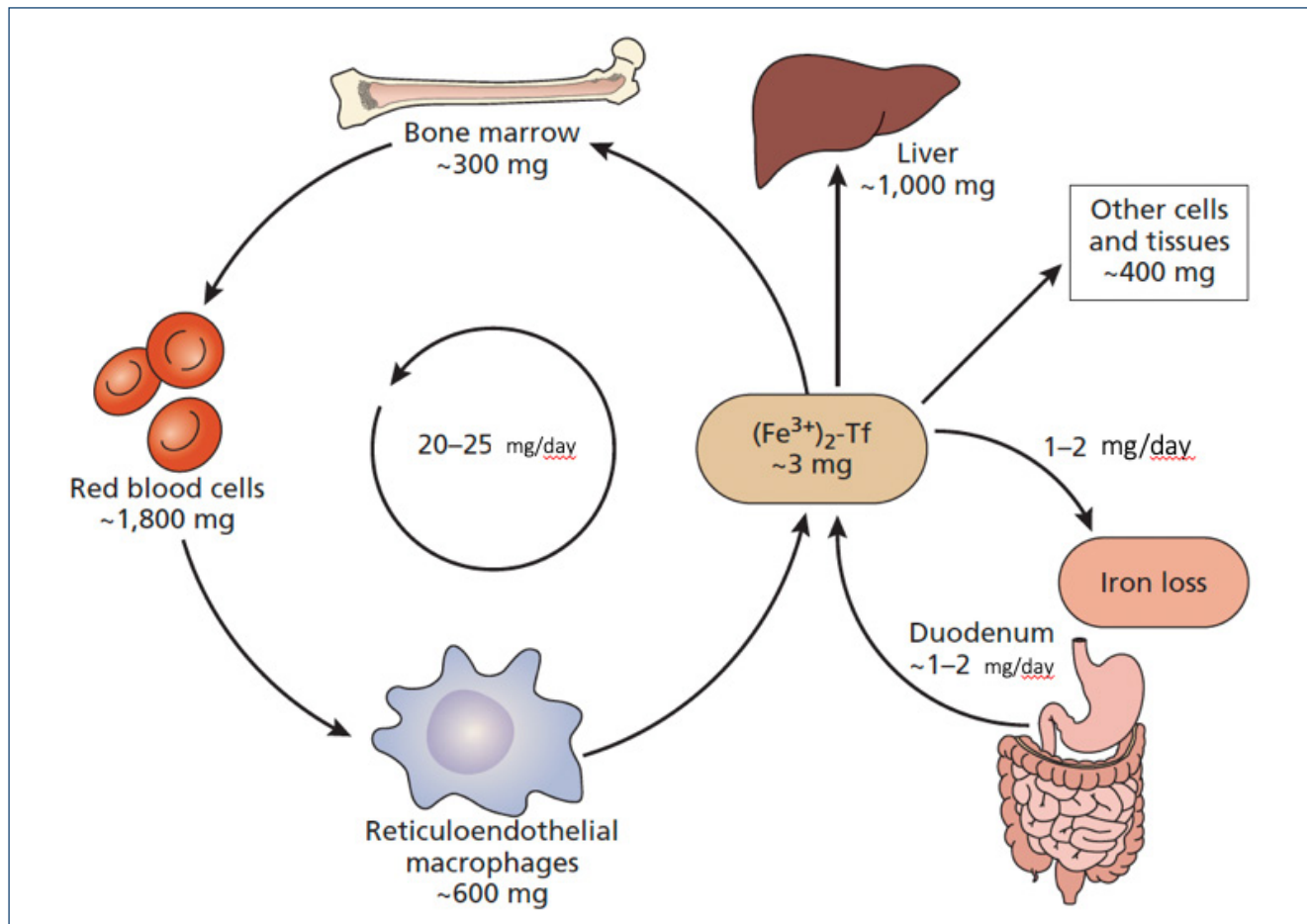


Figure 1. Body iron homeostasis. Plasma iron levels are maintained in a relatively narrow range. Iron circulates in plasma bound to transferrin, which maintains iron in a soluble form, serves as a major route of entry for iron into cells (via the transferrin receptor TfR1), and limits the generation of toxic radicals. The homeostatic system responds to signals from pathways that consume iron (e.g., erythropoiesis) and sends signals to the cells that supply iron to the blood stream. Iron is released into the circulation from duodenal enterocytes, which absorb 1–2 mg of dietary iron per day, and from macrophages, which internally recycle 20–25 mg of iron per day from senescent erythrocytes. While the body regulates processes of iron absorption, storage, and recycling, there is no process for excreting excess iron. Redrawn from Hentze et al.⁵

gastrointestinal (GI) iron absorption. Transferrin production increases in the liver and decreases the levels of iron-bound transferrin in the plasma in ID, further reducing hepcidin levels⁶ (Figure 2).

Unlike absolute ID, FID is a state of imbalance between iron demand and serum iron availability, and it may occur despite adequate body iron stores. FID is most frequently observed in the setting of systemic inflammation and/or infection, in which inflammatory cytokines stimulate increased hepcidin production and thus impair iron absorption from the gut and facilitate iron trapping in macrophages by degrading ferroportin. By reducing iron bioavailability, iron-deficient erythropoiesis occurs. Cytokines may also have an impact on ferroportin production and cellular iron transport through hepcidin-independent pathways, dampen endogenous erythropoietin activity, and shorten erythrocyte life span⁶ (Figure 2).

IRON DEFICIENCY/IRON DEFICIENCY ANEMIA IN WOMEN ACROSS THEIR VARIOUS STAGES OF LIFE

Unfortunately, ID and IDA are mistakenly believed to be benign conditions, unaware of IDA's significant effects on physical and cognitive functions, quality of life, morbidity, and mortality^{7,8}.

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN WOMEN OF REPRODUCTIVE AGE

Although ID is most common in low-income countries, recent data show that 40–50% of European nonpregnant women have low iron stores^{2,4}. Women are known to have a much higher IDA prevalence compared to men of the same age; the prevalence rate is about 10 times higher than males. This difference

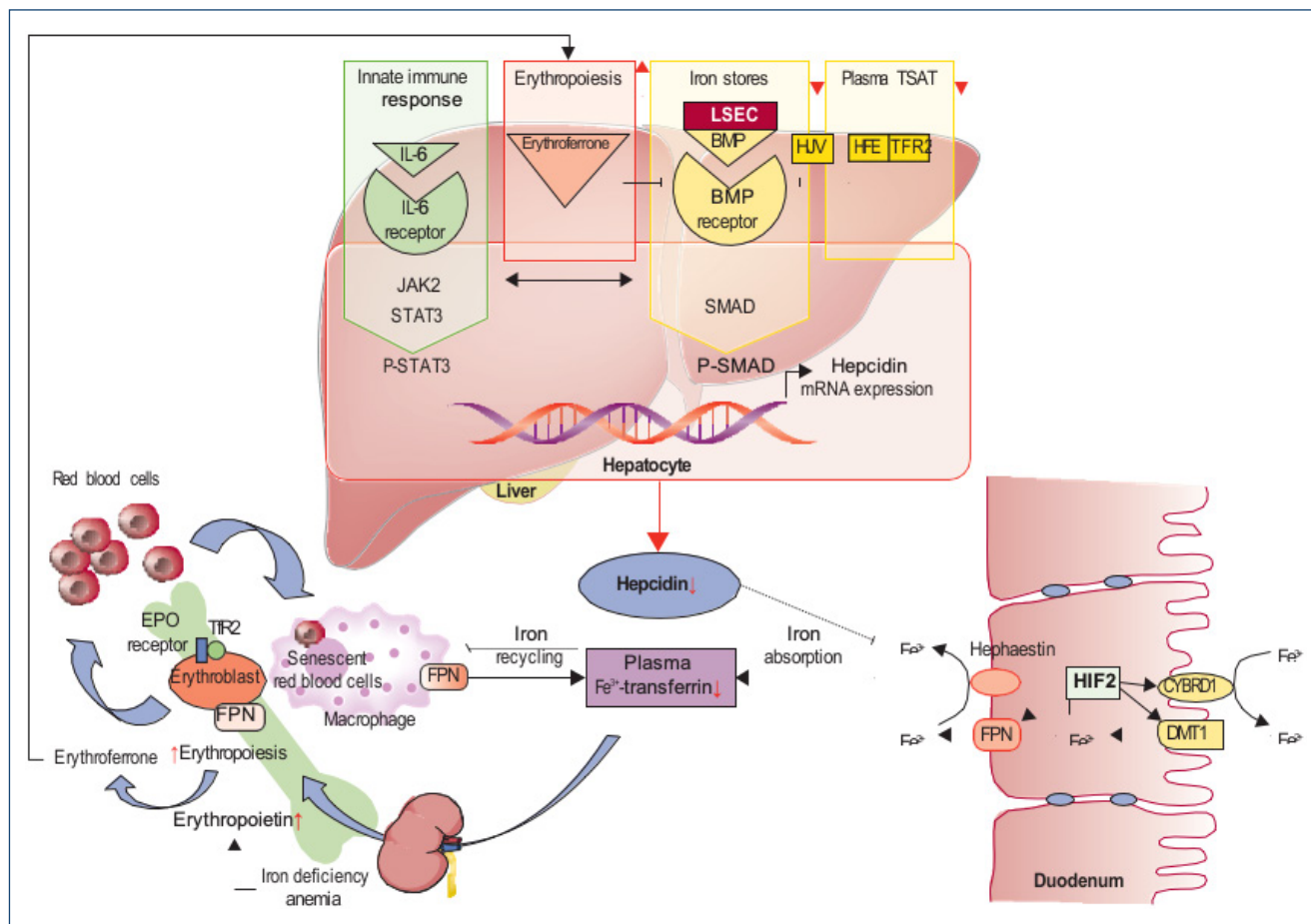


Figure 2. Coordinated homeostatic response to absolute and functional iron deficiency⁶. Modified from Pasricha et al.⁶. Red arrows refer to physiological stimuli (e.g., absolute iron deficiency or increased erythropoiesis) that suppress hepcidin expression. During absolute ID, decreased circulating transferrin saturation and liver iron storage suppress hepcidin transcription via reduced BMP-SMAD signaling (yellow pathway). As a consequence, duodenal and macrophage FPN proteins are stabilized, facilitating dietary iron absorption in duodenal enterocytes and release of iron from macrophages of the reticuloendothelial system, thereby increasing iron concentrations in the plasma. Additionally, reduced iron concentration in duodenal enterocytes is sensed by the iron-dependent prolyl hydroxylase domain enzymes that increase the stability of the transcription factor HIF-2, which regulates transcription of apical (CYBRD1 and DMT1) and basolateral (FPN) iron transport machinery. During iron deficiency, in most cell types, the IRP/IRE system stabilizes mRNAs of proteins crucial for iron uptake (e.g., TfR1 and DMT1) and suppresses the synthesis of proteins involved in the storage (ferritin), utilization (cytoplasmic and mitochondrial iron-containing proteins), and export (FPN) of iron. In functional iron deficiency, inflammation increases hepatic hepcidin expression via IL6-JAK2-STAT3 signaling (green pathway), causing reduced FPN abundance and function on cells, depriving the plasma of iron. In response to IDA, the kidney produces erythropoietin, which stimulates erythropoiesis. Erythroblast erythropoietin sensitivity can be modulated by Tfr2. In absolute iron deficiency, erythroblasts, and erythrocytes donate iron through FPN-mediated iron export. Increased erythropoiesis (e.g., during recovery from anemia) causes secretion of erythroferrone, which suppresses hepatic hepcidin expression via inhibition of BMP-SMAD signaling (red pathway). LSEC, liver sinusoidal endothelial cell. P, phosphorylated. TSAT, transferrin saturation.

is mostly due to regular blood loss during menstruation, which is often associated with low iron intake. Adolescent girls are particularly vulnerable to this condition because of the elevated iron requirement for rapid growth and menstrual blood loss. Furthermore, several conditions can play a determinant role in favoring ID in women, such as chronic gynecologic bleeding due to uterine fibroids, endometriosis, adenomyosis, or endometrial hyperplasia. Moreover, intestinal malabsorption problems, frequent blood donation, and benign and malignant GI lesions are other causes of IDA in women⁸⁻¹¹.

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN WOMEN WITH HEAVY MENSTRUAL BLEEDING

Heavy menstrual bleeding can be defined as a total blood loss per menstrual cycle that regularly exceeds 80 mL. However, a definition requiring quantification of blood loss is only useful for research studies and accurate assessments of menstrual blood flow. The UK-based National Institute for Health and Care Excellence (NICE) has suggested that HMB should also be diagnosed when there is regularly excessive menstrual blood

loss that “affects the physical, social, emotional or material quality of life of the patient”¹².

HMB is estimated to affect approximately 18–38% of women of reproductive age and may increase in prevalence for women approaching menopause. However, there is considerable variability in the reporting of HMB, and the condition is likely to be underdiagnosed^{12,13}.

Prolonged blood loss, such as a menses duration of more than 7 days, or moderate blood loss in combination with an iron-deficient diet, such as often occurs in adolescents and vegans, can also contribute to the risk of ID in women. Women with HMB lose on average five to six times more iron per menstrual cycle than women with normal blood loss, resulting in totally depleted iron stores^{14,15}.

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN PREGNANT WOMEN

The physiological iron demand dramatically increases in pregnancy (approximately 1,000–1,200 mg with an average weight of 55 kg), despite the temporary respite from iron losses incurred during menstruation. This quantity includes almost 350 mg associated with fetal and placental growth, about 500 mg associated with expansion in red cell mass, and around 250 mg associated with blood loss at delivery. In the course of gestation, iron needs present a variation with a growing trend; in fact, there is a lower iron necessity in the first trimester (0.8 mg/day) and a much higher need in the third trimester (3.0–7.5 mg/day). At the beginning of pregnancy, approximately 40% of women show low or absent iron stores, and up to 90% of women have iron reserves of <500 mg, which represent an insufficient amount to meet the increased requirements^{10,16}. Surprisingly, it is uncommon for pregnant women to be checked for ID unless anemic, and low Hb concentration alone may miss up to 55% of ID pregnant women when other iron parameters are not added to screening laboratory tests^{10,16}.

APPROACH TO IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA

The diagnostic approach for managing ID and IDA involves a three-step approach: (1) identification, (2) investigation, and (3) iron repletion¹⁷.

Step 1. Identification of iron deficiency/iron deficiency anemia

Although ID is by far the most common cause of anemia, laboratory evaluation is fundamental for a definitive diagnosis of

ID and IDA in order to provide appropriate treatment. As the etiology of anemia includes various causes, the diagnosis cannot be based only on Hb values.

The initial laboratory tests that are essential for the etiological investigation of anemia are as follows:^{6,9,10,14,17}

- Complete blood count including red cell indices.
- Reticulocyte count—to assess erythropoietic activity of the bone marrow in a case of anemia.
- Analysis of peripheral blood smear can provide important information regarding the underlying cause of anemia.
- Serum iron, total iron binding capacity, and transferrin saturation (TSAT)—result of the equation: (serum iron ÷ the total iron binding capacity) multiplied by 100.
- Serum ferritin (SF)—the most reliable initial test for diagnosing ID.

The reticulocyte count provides important information about the level of erythropoietic activity in the bone marrow and is an integral part of the screening process for every patient with anemia. In addition to the number of reticulocytes in absolute values, the Hb content of reticulocytes can provide additional information regarding impaired hemoglobinization of erythrocytes and is a valuable and early indicator of ID⁵⁻⁷.

Ferritin is an intracellular iron storage protein that correlates with the body’s iron stores in the absence of threshold of ferritin <30 mg/L, achieves a higher sensitivity (92%), while maintaining a high 98% specificity for the diagnosis, and is thus commonly used. Ferritin <30 mg/L and TSAT <20% have been recommended for the diagnosis of ID and, when these parameters are associated with anemia, for IDA^{7,14,17}.

The diagnosis of ID becomes more challenging with concomitant inflammatory conditions because ferritin is an acute-phase reactant that increases with inflammation. In these circumstances, TSAT <20% and higher ferritin thresholds (between 30 and 100 mg/L) can be used for the diagnosis of IDA^{9,14,17}. An earlier marker of ID is the reticulated hemoglobin content (CHr), which is decreased (<29 pg) in ID (Table 1). The evaluation of C-reactive protein (CRP) levels may assist in obtaining the correct diagnosis, excluding infections or inflammation. If the CRP value is elevated, re-evaluation of the SF level is recommended after the normalization of CRP concentration.

Hepcidin is the main protein that controls plasma iron transit through its binding to ferroportin, the only iron-exporting protein present in the cell membrane of macrophages, enterocytes, hepatocytes, and placental syncytiotrophoblasts. After the formation of the hepcidin-ferroportin complex, it is internalized and degraded in lysosomes (Figure 2). Despite its

relevance in the differential diagnosis of ID, the measurement of hepcidin (in serum or urine) by mass spectrometry (the most reliable and reproducible method) still has a high cost, which limits its use in daily clinical practice.

Step 2. Investigation of iron deficiency/iron deficiency anemia^{6-11,14,17,18}

ID and IDA are not a final diagnosis; rather, they are indicative of an underlying etiology that is decreasing iron availability and/or increasing iron needs. To effectively manage ID/IDA, the underlying etiology must be identified and, if possible, treated (Table 2).

Step 3. Iron repletion

The treatment of ID/IDA includes oral iron, IV iron, and RBC transfusions. The cause and severity of anemia, comorbidities, the time remaining until delivery, and patients' wishes are important factors that must be considered when deciding the therapeutic approach^{6-11,14,17,18}.

RED BLOOD CELLS TRANSFUSION

Recommendations from the American Society of Hematology and American Association of Blood Banks campaigns across jurisdictions and specialties have highlighted the importance of restrictive

Table 1. Differential diagnosis of types of iron deficiency^{6-8,14,18,36}.

Parameter	ID	IDA	FID	IDA+FID
Symptoms	Asymptomatic or mild symptoms of anemia	Mild-severe symptoms of anemia	Symptoms of the underlying disease, symptoms of anemia	Symptoms of the underlying disease, symptoms of anemia
Hemoglobin	NI/↓	↓	↓	↓
MCV	NI/↓	↓	NI/↓	↓
TSAT	20-45%	<20%	<20%	<20%
Ferritin, ng/mL	<30	<30	NL/	NL/
Reticulated hemoglobin content	↓	↓	↓	↓
Hepcidin	NI/↓	↓		NI/↓

Table 2. Main causes of iron deficiency^{6-11,14,17,18}.

Increased iron requirement	Excessive loss of iron (blood loss)
<ul style="list-style-type: none"> • Growth* • Menstruation** • Pregnancy*** • Lactation • ESA therapy 	<ul style="list-style-type: none"> • Gastrointestinal bleeding • Esophageal: varicose veins, carcinoma, ulceration, reflux esophagitis • Gastric: polyp, cancer, ulcer, gastritis, angiodysplasia, telangiectasia, antral gastric vascular ectasia, associated with the use of aspirin, nonsteroidal anti-inflammatory drugs, anticoagulants, antiplatelet agents • Small intestine: inflammatory bowel disease, duodenal ulcer, Ancylostoma duodenale and Necator americanus infection, cancer, polyp, angiodysplasia, telangiectasia, Meckel's diverticulum, associated with intense exercise, milk allergy • Large intestine: cancer, polyp, diverticular disease, angiodysplasia, inflammatory bowel disease, Heyde's syndrome[#] • Anus: Hemorrhoid • Entire gastrointestinal tract: hereditary hemorrhagic telangiectasia • Gynecological bleeding: abnormal uterine bleeding^{##}; uterine cancer or other cancers of the reproductive tract, intrauterine device • Urinary bleeding: cancer: kidney, bladder, prostate • Intravascular hemolysis: PNH, gait hemoglobinuria, thrombotic microangiopathy, gait hemoglobinuria, malaria • Respiratory bleeding: hemoptysis (cancer, infection) • Blood donation • Exercise • Excessive iatrogenic blood loss^{###}
Inadequate dietary intake and/or defective absorption of iron	
<ul style="list-style-type: none"> • Low bioavailability of Fe diet[@] • Vegetarian or vegan practice • Inflammatory bowel disease • Celiac disease • Parasitosis • Obesity • Post-gastroplasty (gastric bypass) • Post-gastrectomy • Atrophic gastritis • Helicobacter pylori infection • Medications: antacids, proton pump inhibitors, calcium, tannin • IRIDA^{@@} 	

ESA: erythropoiesis-stimulating agents; *During early childhood and adolescence; **Physiological blood loss exceeding daily iron intake; ***Additional iron requirement for each pregnancy of approximately 1,000 mg for expansion of maternal erythrocyte mass and placental and fetal development; @Resulting from poverty, especially in low-income countries, early cessation of breastfeeding, and inadequate transition diet; @@IRIDA, iron-refractory iron deficiency anemia caused by mutations in the TMPRSS6 gene; #Heyde's syndrome (severe aortic stenosis, syndrome type 2 acquired von Willebrand disease, angiodysplasia and ECD); ##Abnormal uterine bleeding usually related to uterine fibroid, adenomyosis, endometrial hyperplasia, or dysfunctional uterine hemorrhage fibroid, exacerbated by bleeding disorders (von Willebrand disease, haemophilia A or B, and platelet dysfunction); PNH: paroxysmal nocturnal hemoglobinuria; ###Excessive blood collection for diagnostic tests and iron losses during hemodialysis.

RBC transfusion and promoted the use of alternative therapeutic options to transfusion (egg, oral, or IV iron supplementation, recombinant erythropoietin) when available and appropriate, in order to avoid transfusing RBCs for IDA without hemodynamic instability. Therefore, RBC transfusion for severe IDA should be restricted for cardiovascular compromise and/or debilitating symptoms, when a rapid correction of anemia is clinically required. Unfortunately, blood transfusion for the correction of anemia is still a frequent practice observed in many centers, especially in the postpartum period¹⁹⁻²¹.

ORAL IRON--CURRENT PRACTICAL RECOMMENDATIONS

Oral iron supplementation remains the standard first-line therapy for treating ID and IDA. Oral iron is inexpensive, easy to access, available without a prescription, and, when tolerated and taken properly, is highly effective in correcting ID²². Oral iron compounds vary widely according to salt type, formulation, chemical state (ferrous or ferric form), elemental iron content, bioavailability, efficacy, adverse events (AEs), and cost. The four main iron supplements commercialized in Brazil are listed in Table 3^{22,23}.

Historically, the recommended dose for the treatment of adult individuals with IDA has always been 100–200 mg of elemental iron per day, divided into two to three intakes, with daily doses greater than 200 mg not being recommended. In the past decade, with advances in the knowledge and importance of hepcidin in body iron homeostasis and studies with radioisotopes, and with the objective of overcoming the inhibitory action of hepcidin, reducing AEs, and improving tolerance and adherence to oral iron, new recommendations have been proposed for treatment with oral iron^{24,25}.

ORAL IRON PROPHYLAXIS OF IRON DEFICIENCY/IRON DEFICIENCY ANEMIA IN PREGNANCY

There is poor evidence about the effect of iron prophylaxis in pregnancy in determining a reduction in global ID prevalence and, consequently, a decrease in maternal and fetal complications. Therefore, the WHO promotes daily iron supplementation during pregnancy for women who live in areas with a high prevalence of ID because the administration of prophylactic iron to women with low iron stores represents a significant benefit. Current guidelines indicate 60–120 mg of elemental iron per day.

IV IRON

IV iron has traditionally been used for unresponsiveness to or intolerance of oral iron replacement therapy or for patients for

whom rapid iron replacement (e.g., preoperative ID or symptomatic anemia, bleeding due to placenta praevia, and advanced gestational age) is desired. IV iron therapy is indicated in pregnancy from the second trimester onward^{26,27}.

IV iron administration bypasses the absorption difficulties associated with oral iron and represents an optimal alternative to oral iron therapy. 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^{9,10,28,29}. In addition, IV iron may be useful in the treatment of AI; high single doses of IV iron may overcome the block caused by hepcidin in patients with this condition^{30,31}.

Despite the standard approach of using oral iron as first-line therapy for ID/IDA, the growing evidence for the greater efficacy and safety of IV preparations has convinced many experts that IV iron is frequently the preferred treatment^{30,31}.

The reduced number of IV iron administration needed to deliver the required total iron dose is much more convenient, potentially more cost-effective, and may be particularly suitable for the treatment of IDA, especially in the obstetrics and gynecology population when the vast majority of patients are being treated on a strictly outpatient basis, such as women with HMB and IDA, when supplemental oral iron therapy is often insufficient to keep pace with ongoing iron losses associated with recurring menses, late pregnancy, or severe anemia. IV iron has superior efficacy compared with oral iron, with significantly more women reaching target Hb levels and substantial Hb increases³⁰⁻³⁴.

The current recommendation for the treatment of IDA with IV iron as well as the iron formulations available in Brazil (ferric saccharate, ferric carboxymaltose, and ferric derisomaltose) are summarized in Table 4³⁰⁻³⁴.

CHRONIC IRON NEED

There are many populations who will require ongoing iron supplementation beyond initial iron repletion as a maintenance iron therapy. Such populations include those with inflammatory bowel disease and malabsorption (e.g., bariatric surgery) or ongoing GI blood loss (e.g., abnormal uterine bleeding refractory to or awaiting gynecologic intervention).

Current guidelines recommend routinely rechecking complete blood count, reticulocytes, reticulated-Hb content, and iron parameters 3–6 months after initial iron repletion to determine whether ongoing iron supplementation is required and to establish the optimal route, dose, and frequency. For some patients (e.g., women with HBM),

asymptomatic outpatients with mild ID/IDA in whom there is no inflammation and in whom oral iron is well tolerated, we are successful in maintaining normal iron stores and Hb levels using once-per-day or every-other-day oral iron. In

other patients, a regimen of once per month, once every 3 months, or once every 6 months IV of iron is required, with the goal of maintaining normal iron status (ferritin >30 mg/L; TSAT >20%)^{14,10,26}.

Table 3. Current recommendation for the treatment of iron deficiency with oral iron^{22-25,37,38}.

Current recommendation for the treatment of iron deficiency with oral iron	
•	Single daily dose of oral iron is preferable to divided doses because divided doses twice or three times a day are physiologically ineffective.
•	Ferrous salts should be taken 1 h before meals or between meals or before bedtime (time of greatest gastric acid production).
•	Ferric salts can be given during or after a meal.
•	The major problem with oral iron supplements is that 20–56% of patients cannot tolerate them because of GI AEs, including abdominal distress, nausea, vomiting, constipation, diarrhea, metallic taste, and dark stool; and the discontinuation of treatment is up to 20%.
•	It is important for prescribers to inform patients of these potential AEs prior to commencing oral iron therapy and to encourage an open dialogue so that should negative effects occur, alternative therapies can be provided.
•	The common practice of administering ferrous salts with food in an attempt to alleviate GI AEs can effectively decrease absorption by 40–66%.
•	AEs rate related to oral iron are dose-dependent. It is important for the physician to be aware of the amount of elemental iron present in different medications, as this varies considerably according to the compound used or available.
•	Doses up to 100 mg of elemental iron should be prescribed once a day, daily. Doses > 100–200 mg of elemental iron should be prescribed on alternate-day regimen to optimize iron absorption, reduce the rate of GI AEs, and improve treatment tolerance. The rate of iron absorption is 40–50% greater on alternate days versus consecutive days for doses between >100 and 200 mg of elemental iron.
•	Avoid daily dose of elemental iron >200 mg
•	With consistent oral iron supplementation, reticulocytosis starts in 4–5 days, and Hb begins to improve by the second week. The main criteria for a good response to treatment are an increase of at least 2 g/dL is expected after 3–4 weeks of treatment.
•	As an overarching principle, with any IDA patient, provide enough iron to not only correct the Hb deficit, but enough to provide measurable storage iron as reflected by the SF. Then, SF can be monitor for ongoing iron losses and, with appropriate administration of supplemental iron, prevent ID and IDA.
•	Oral iron therapy is often required for at least 3–6 months, depending on the intensity of the ID, continuity of blood loss, occurrence of AEs, and consequently adherence to treatment. The goal of iron replacement is not only to correct the Hb deficit but also to provide enough iron to replete iron stores and normalize ferritin levels (serum ferritin >30 ng/mL and TSAT >20%).
•	Periodic monitoring (SF and TSAT) and retreatment prior to the recurrence of ID are recommended among high-risk populations: pregnant women (at the first prenatal visit and in each trimester during pregnancy) and among specific groups of nonpregnant women of childbearing age.
•	There are no biochemical markers to predict the likelihood of response to oral iron. In addition to the problem of AEs, impaired iron absorption such as inflammatory bowel disease and other malabsorption states, prior gastric bypass surgery, and concomitant administration of drugs can inhibit iron absorption and decrease responsiveness to oral iron.
•	Intake of citrus fruits containing vitamin C (orange, lemon, and acerola) before or during a meal increases iron absorption. Multivitamins containing divalent metals (zinc, copper, and manganese) and various dietary components (phytates, polyphenols, calcium, and phosphates) reduce the absorption of ferrous salt. Therefore, it is recommended that they be administered separately from other vitamin supplements.

Comparison between the four main iron supplements marketed in Brazil

Variable	Ferrous Sulfate	Ferric salts		
		Ferripolymaltose	Aminocheated Iron	Ferrocabonyl
Administration	Preferably with an empty stomach	During or after meal		
Efficiency	High	Intermediate to high		
Rate of Adverse events	High (35–55%)	Intermediate (15–35%) to low (10–15%)		
Treatment tolerance	Low	Intermediate to high		
Quantity of elemental iron	20%	30%	20%	33%

Definition of treatment failure with oral iron:
Hb ≤2 g/dL after 3–4 weeks of treatment with 100–200 mg of elemental iron/day.

Most frequent causes of treatment failure with oral iron:

- Continuing blood loss due to failure to identify bleeding and/or iron absorption disorder.
- Medication inappropriately used--poor adherence to treatment due to gastrointestinal AEs and/or inadequate dose and/or insufficient duration.
- Coexisting disease interfering with the response (reducing iron absorption and/or favoring bleeding) to oral iron treatment--chronic kidney disease associated with inflammatory or infectious disease.
- Diseases associated with iron absorption disorder--celiac disease, autoimmune atrophic gastritis, and Helicobacter pylori infection; incorrect diagnosis.
- Combined nutritional deficiencies.

Table 4. Current recommendation for the treatment of iron deficiency with IV iron^{30-35,39-42}.

Main indications for IV iron treatment		
<ul style="list-style-type: none"> • Oral iron intolerance determined by the occurrence of AEs. • Unsatisfactory response with oral iron due to intestinal absorption disorder associated with conditions such as: gastric bypass, gastrectomy, and chronic gastrointestinal inflammatory disease (H. pylori infection, Celiac disease, Crohn's disease, ulcerative colitis, and atrophic gastritis). • Recurrent bleeding (gastrointestinal and gynecological) in which the amount of iron absorbed orally is not sufficient to meet the demand resulting from excessive iron loss. • Rapid iron replacement in order to reduce transfusion requirement in patients with IDA scheduled for medium to major elective surgery, including childbirth and the puerperium. • Faster normalization of iron stores avoiding prolonged use of oral therapy and its AEs. • Patients with nondialytic chronic kidney disease with serum ferritin < 100 ng/mL or on hemodialysis with serum ferritin < 200 ng/mL in order to ensure and optimize the response to erythropoietin administration. • Special situations such as: pre-deposit autotransfusion programs and religious issues (Jehovah's Witness patients). 		
Goals of IV iron treatment		
<ul style="list-style-type: none"> • Faster correction of anemia (an increase of 2–3 g/dL of Hb after 4 weeks of treatment) and iron stores. • Reduce/eliminate the need for blood transfusions. • Optimize the use of erythropoietin (cancer and chronic kidney disease). 		
Main practical guidelines for the use of IV ferric saccharate		
<ul style="list-style-type: none"> • To calculate the total dose of iron (in mg) to be replaced, the Ganzoni formula can be used: $\text{body weight (kg)} \times (\text{target Hb} - \text{current Hb}) \times 2.4 + 500$. • There is no need to perform a test dose before application. • Dilute the compound only in 0.9% saline solution (SF). Do not dilute in glucose solution. • Dilute each ampoule (5 mL, 100 mg) in at least 100 mL of saline solution. • For each solution containing 100 mg of ferric saccharate, the infusion time should be at least 15 min. Therefore, the infusion of the solution containing 200 mL (or more) of SS and 200 mg of ferric saccharate should be done within 30–60 min. • It is important to respect the drug infusion time. • Respect the interval between applications, which is at least 24 h. • Respect the maximum dose limit per application, which is 200 mg (two ampoules) and the maximum weekly dose, which is 600 mg. 		
Main practical guidelines for the use of IV ferric carboxymaltose		
<p>Ferric carboxymaltose (FCM) has been available for over a decade and is indicated for the treatment of IDA in various clinical situations. It is an innovative iron complex composed of a core of ferric hydroxide, surrounded by a layer of carbohydrate (maltose) that combines the advantages of iron dextran (high stability) with the advantages of ferric saccharate (low immunogenicity). After administration, FCM is phagocytosed by macrophages, especially in the bone marrow; maltose is degraded and iron molecules are released to form the intracellular pool of iron in the form of ferritin or destined for erythropoiesis via plasma transferrin. Another important advantage of this product is its convenient dosage, that is, FCM can be administered in high doses (dose of up to 1,000 mg of iron or maximum dose of 15 mg/kg per application) IV in at least 15 min and without the need for a test dose.</p>		
Hemoglobin (g/dL)	Total dose of ferric carboxymaltose	
	Body weight >35 and <70 kg	Body weight ≥70 kg
<10	1,500 mg	2,000 mg
≥10	1,000 mg	1,500 mg
<ul style="list-style-type: none"> • There is no need to perform a test dose before the first infusion. • Dilute the compound only in 0.9% saline solution (SF), 50–100 and 200 mL for 500 and 1,000 mg of FCM, respectively. Do not dilute in glucose solution. • Dilute each ampoule (10 mL, 500 mg) in at least 100 mL of saline solution. • The recommended minimum infusion rate is 100 mg/min. Infusion time is, at least, 6 min for up to 500 mg and 15 min for doses between >500 and 1,000 mg. • The maximum dose per application should not exceed 1,000 mg (>15 mg/kg body weight) of iron per application. • Doses >15 mg/kg should be divided into 2 infusions 7 days apart. Do not administer more than 1,000 mg of FCM per week. Therefore, the interval between 2 and 3 applications of 1,000 mg is at least 7 days. • FCM is for IV use only and should not be administered subcutaneously or intramuscularly. • Ferinject® 100 mg/mL solution for infusion (5 or 10 mL vial). 		

Continue...

Table 4. Continuation.

Main practical guidelines for the use of IV ferric derisomaltose		
<p>Ferric derisomaltose (FD) is available in Europe and has recently been licensed in the US, Australia, and Brazil. Like FCM, it is an innovative iron complex composed of a core of ferric hydroxide surrounded by a layer of carbohydrate (maltose) that combines the advantages of iron dextran (high stability) with the advantages of ferric saccharate (low immunogenicity); it can be administered in high doses (maximum allowed dose of 20 mg of iron/kg of body weight). If the total iron dose calculated is >20 mg/kg/weight, the supplementary dose should be performed after ≥7 days.</p>		
Hemoglobin (g/dL)	Total dose of ferric derisomaltose	
	Body weight <70 kg	Body weight ≥70 kg
≥10 and <12	1,500 mg	2,000 mg
<10	1,000 mg	1,500 mg
<ul style="list-style-type: none"> Whenever possible, administer the total dose in the first infusion as long as it does not exceed the maximum allowed dose (>20 mg of iron/kg of body weight). If total dose >20 mg/kg/weight: second dose after ≥7 days. Dilution ≥1 mg/mL for stability reasons. For a 500 mg dose, dilute 100 mL in saline solution and infuse the solution in at least 15 min. For doses ≥1,000 mg, dilute 200 mL in saline solution and infuse the solution over at least 30 min. Monofer® solution for infusion of 100 mg/mL in packaging containing 1 vial of 5 or 10 mL. 		
<p>Contraindications to the use of IV iron</p> <ul style="list-style-type: none"> Any type of anemia unrelated to iron deficiency. TSAT >45%. Serum ferritin ≥500 ng/mL, regardless of TSAT value. Patients with acute infection, especially in the presence of bacteremia/septicemia. Patients with known hypersensitivity to iron or any component of its formulation. 		
<p>Warnings and recommendations with IV iron</p> <ul style="list-style-type: none"> The use of IV iron should be done with caution in patients with asthma, eczema, or atopic allergies, especially in those with a past history of moderate-to-severe hypersensitivity reactions, including anaphylactic reactions. In these cases, the use of antiallergic drugs (IV diphenhydramine) and/or corticosteroid therapy (IV hydrocortisone) as premedication is recommended. Due precautions must be taken to avoid venous extravasation during drug administration, which can cause local changes such as: pain, irritation, and browning of the skin. If this occurs, administration of the product must be stopped immediately. The use of IV iron should be avoided in patients with severe hepatic impairment. The use of IV iron should be avoided in pregnant women ≤13 weeks of gestation. To date, FCM and FD are not recommended in children or adolescents (<18 years). IV oral should not be administered concomitantly with oral iron. Regardless of the product used, it is recommended that IV iron be applied in a hospital environment or, preferably, in clinics or infusion units with experience in IV drug administration, by duly trained nursing professionals with medical supervision. Observation of the patient for at least 30 min after the end of IV iron infusion is recommended. 		
<p>When and how to assess response to IV iron treatment</p> <p>It is recommended to carry out complete blood count, reticulocytes, serum iron, total binding capacity of iron, and ferritin after 4–6 weeks of administration of the total dose of iron calculated for the patient.</p>		
<p>IV iron safety profile</p> <ul style="list-style-type: none"> Minor reactions (e.g., headache, symptomatic hypotension, back pain, heartburn, chest tightness, dyspnea, nausea, tachycardia, rash, and vomiting) are due to labile free iron and consist of pressure in the chest or back or facial flushing—symptoms not seen with severe hypersensitivity. Furthermore, premedication with antihistamines can cause somnolence, diaphoresis, tachycardia, and hypotension, which may be attributed to the intravenous iron. Intervention with antihistamines or vasopressors can convert these minor reactions, which usually resolve in minutes without therapy, into hemodynamically significant AEs, ostensibly due to the intravenous iron. FCM has a lower risk of hypersensitivity, but a higher incidence of hypophosphatemia, which in most cases is not severe, is temporary and asymptomatic. Although very rare, severe hypersensitivity reaction can occur with IV iron. 		

MANAGEMENT OF IRON DEFICIENCY ANEMIA IN PREGNANCY

The laboratory diagnosis of ID/IDA, including Hb concentration and serum levels of biochemical markers of iron status, and the correct treatment of IDA are relevant, especially during pregnancy (Figure 3).

MANAGEMENT OF PREOPERATIVE IRON DEFICIENCY/IRON DEFICIENCY ANEMIA

Iron repletion is an important component of patient blood management (PBM), a multidisciplinary strategy that aims to conserve blood and optimize the use of blood products by

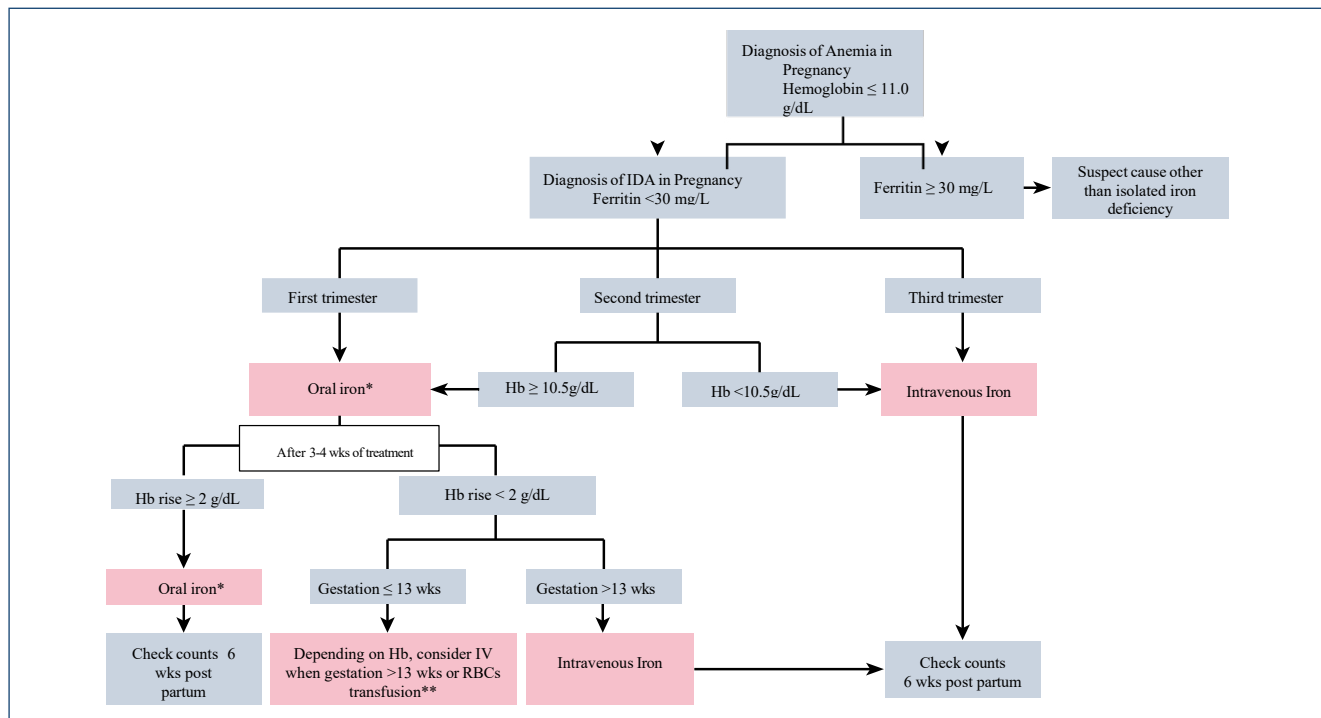


Figure 3. Algorithm of suggested approach to diagnosis and management of iron deficiency anemia in pregnancy. Modified from Achebe et al.⁹ *Oral iron treatment (doses up to 100 mg of elemental iron, prescribed once a day, daily; or doses >100–200 mg of elemental iron, prescribed alternate-day regimen) should not be interrupted once hemoglobin > 11 g/dL is achieved, but rather supplementation should continue to replenish iron stores (Ferritin >30 ng/mL), generally for at least 2–3 months, and until 6 weeks postpartum). **Red blood cells transfusion for severe iron deficiency anemia should be restricted for cardiovascular compromise and/or debilitating symptoms, when a rapid correction of anemia is clinically required.

optimizing and preserving the patient's own blood. Recently published recommendations from the 2018 Frankfurt Consensus Conference on PBM highlighted the importance of (1) early detection and management of preoperative anemia, given its recognized associations with poor outcomes, including mortality, and (2) use of iron supplementation in adults with IDA who are awaiting elective surgery. The care of women with HMB would involve treatment of the underlying cause of the excessive bleeding and minimize blood loss in the perioperative setting³⁵.

CONCLUSION

- ID and IDA are the most debilitating nutritional deficiencies worldwide in the twenty-first century,

affecting almost a third of the global population, particularly among women of all ages, with potentially serious and long-lasting consequences.

- Although ID is by far the most common cause of anemia, laboratory evaluation and etiological cause investigations are fundamental for a definitive diagnosis of ID and IDA in order to provide appropriate treatment.
- Oral iron supplementation remains the first-line therapy for both prophylaxis and treatment of ID/IDA.
- IV iron administration is currently more widely used as a result of the improved safety profile and high effectiveness of last-generation compounds.

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