JAMA | Review

Iron Deficiency in Adults
A Review

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IMPORTANCE Absolute iron deficiency, defined as low iron stores with or without anemia, affects approximately 2 billion people worldwide and 14% of adults in the US. Iron-deficiency anemia, defined as low hemoglobin due to low iron stores, affects approximately 1.2 billion people worldwide, including 10 million in the US.

OBSERVATIONS Absolute iron deficiency progresses from low iron stores to iron-deficiency anemia. Individuals with nonanemic iron deficiency or iron-deficiency anemia may be asymptomatic or experience fatigue, irritability, depression, difficulty concentrating, restless legs syndrome (32%-40%), pica (40%-50%), dyspnea, lightheadedness, exercise intolerance, and worsening heart failure (HF). Symptom prevalences vary depending on age, comorbidities (eg, chronic kidney disease [CKD], HF), and severity and rate of development of iron deficiency. The most common causes of iron deficiency are bleeding (menstrual, gastrointestinal), impaired iron absorption (atrophic gastritis, celiac disease, bariatric surgical procedures), inadequate dietary iron intake, and pregnancy. In high-income countries, approximately 38% of nonpregnant, reproductive-age women have iron deficiency without anemia and about 13% have iron-deficiency anemia. During the third trimester of pregnancy, iron deficiency affects up to 84% of pregnant women, based on data from high-income countries. Additional risk factors include use of nonsteroidal anti-inflammatory drugs, inflammatory bowel disease (IBD [13%-90%]), and other chronic inflammatory conditions, such as CKD (24%-85%), HF (37%-61%), and cancer (18%-82%). Testing for iron deficiency is indicated for patients with anemia and/or symptoms of iron deficiency (fatigue, pica, or restless legs syndrome) and should be considered for those with risk factors such as heavy menstrual bleeding, pregnancy, or IBD. Iron deficiency is diagnosed by low serum ferritin (typically <30 ng/mL) in individuals without inflammatory conditions or by transferrin saturation (iron/total iron binding capacity × 100) less than 20%. Causes of iron deficiency should be identified and treated. Oral iron (ferrous sulfate 325 mg/d or on alternate days) is typically first-line therapy. Intravenous iron is indicated for patients with oral iron intolerance, poor absorption (celiac disease, post–bariatric surgical procedure), chronic inflammatory conditions (CKD, HF, IBD, cancer), ongoing blood loss, and during the second and third trimesters of pregnancy.

CONCLUSIONS AND RELEVANCE Iron deficiency and iron-deficiency anemia are common conditions that may cause symptoms such as fatigue, exercise intolerance, and difficulty concentrating. Ferritin and/or transferrin saturation are required for diagnosis and screening. Oral iron is first-line therapy for most patients. Intravenous iron is used for individuals who do not tolerate or have impaired absorption of oral iron, those with ongoing blood loss, certain chronic inflammatory conditions (IBD, CKD, HF, cancer), and during the second and third trimesters of pregnancy.

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Iron is an important component of hemoglobin and myoglobin and is used in neurotransmitter synthesis and mitochondrial energy generation. Absolute iron deficiency, typically defined as ferritin less than 30 ng/mL or transferrin saturation (TSAT) less than 20% (calculated as iron/total iron binding capacity × 100), affects nearly 2 billion people worldwide.[1] Based on data from the National Health and Nutrition Examination Survey (NHANES) 2017 to 2020, which included 8021 US adults, approximately 14% (95% CI, 13%-15%) had absolute iron deficiency.[2] Another study using NHANES data from 2003 to 2020 reported that among 3490 nonpregnant females aged 12 to 21 years, the percentage of iron deficiency was 38.6% (95% CI, 35.8%-40.9%), using a 25-ng/mL ferritin cutoff to diagnose iron deficiency.[3] In a study of 644 066 reproductive-age nonpregnant women in Canada, 38.3% had iron deficiency without anemia and 13% had iron-deficiency anemia.[4]

Absolute iron deficiency may be associated with cognitive dysfunction ("brain fog" [decreased concentration/attention]), mood changes (irritability, depression), fatigue, exercise intolerance, worsening heart failure (HF), restless legs syndrome (RLS), and pica (craving nonfood substances, such as ice). If the cause of iron deficiency is not diagnosed and treated, iron-deficiency anemia may develop.[5]

Iron-deficiency anemia, typically defined as ferritin less than 30 ng/mL or TSAT less than 20%, and hemoglobin below the reference range (<12 g/dL in women and <13 g/dL in men), affects more than 1.2 billion people worldwide and approximately 10 million people in the US.[1,6] Individuals with iron-deficiency anemia may have more severe symptoms than those who have iron deficiency without anemia, especially if anemia develops quickly (days to weeks rather than months). The World Health Organization Global Burden of Disease study lists iron-deficiency anemia as 1 of the top 5 causes of years lived with disability.[6]

This Review focuses on the screening, diagnosis, and treatment of absolute iron deficiency with or without anemia. Functional iron deficiency, identified by normal or elevated ferritin levels with low TSAT (<20%),[7] which can result in functional iron-deficiency anemia, also known as anemia of chronic disease, anemia of inflammation, or iron-restricted erythropoiesis, is briefly mentioned.

Methods

PubMed was searched for English-language studies of iron deficiency and its treatment in adults published between January 1, 2014, and November 1, 2024. Guidelines not indexed in PubMed were added. We prioritized systematic reviews and randomized clinical trials (RCTs) and reviewed 350 articles. Of these, 86 were included, consisting of 33 RCTs, 20 interventional trials, 16 observational studies, 10 systematic reviews, 6 guideline documents, and 1 review. Study participants in this Review are described as reported in the original research. For characterizations of sex and gender, terms such as *women*, *females*, and *mothers* follow the primary source.

Discussion and Observations

Pathophysiology

Iron is necessary for the production and function of hemoglobin (which binds oxygen) and myoglobin as well as other cellular processes, including mitochondrial energy production and neurotransmitter synthesis.[8] Without treatment, absolute iron deficiency may progress to severe, symptomatic anemia.

Iron is absorbed from the diet. The most efficiently absorbed form is heme iron, derived from red meat, poultry, and seafood. Nonheme iron is available from legumes and vegetables (eg, dried beans, dark leafy greens) and supplemented cereals. Both forms of iron are absorbed by intestinal enterocytes and transported via the iron exporter ferroportin to circulating transferrin in the blood. Transferrin transports iron to the liver and spleen for storage as ferritin, the primary form of stored iron, and hemosiderin in the bone marrow.[9] Iron is primarily stored in the reticuloendothelial system and salvaged from senescent red blood cells (RBCs) by macrophages. Approximately 1 to 2 mg of iron is lost in sweat and stool daily (**Figure 1**).

Hepcidin, a hormone synthesized predominantly in the liver, regulates iron absorption and storage. Hepcidin blocks ferroportin and promotes its degradation,[10] thereby preventing iron absorption and the release of stored iron from reticuloendothelial cells of the liver, spleen, and bone marrow. Hepcidin decreases when iron stores are low, increasing iron absorption and the release of stored iron. Conversely, hepcidin increases with recent iron intake, adequate iron stores, and inflammation, suppressing iron absorption and ferritin release from storage. When hepcidin is elevated, stored iron is inaccessible for hemoglobin synthesis,[6] and prolonged hepcidin elevation can lead to functional iron deficiency and associated anemia.

Epidemiology and Risk Factors

Absolute iron deficiency results from blood loss, inadequate dietary intake, or impaired iron absorption (**Box 1**). The most common causes of absolute iron deficiency, with or without anemia, in high-income countries are bleeding (menstrual, gastrointestinal [GI]) and pregnancy.[11]

Most diets in high-resource countries contain iron sufficient to prevent iron deficiency, although vegetarian and vegan diets and food insecurity may reduce iron intake below the level needed to maintain iron stores, especially in individuals who are menstruating or pregnant.[12] The recommended daily intake of iron for women is 18 mg/d, of which approximately 10% (1.8 mg/d), is absorbed; the average intake in the US is approximately 13 mg/d for women.[13] Menstruation increases iron requirements to about 2 mg/d.

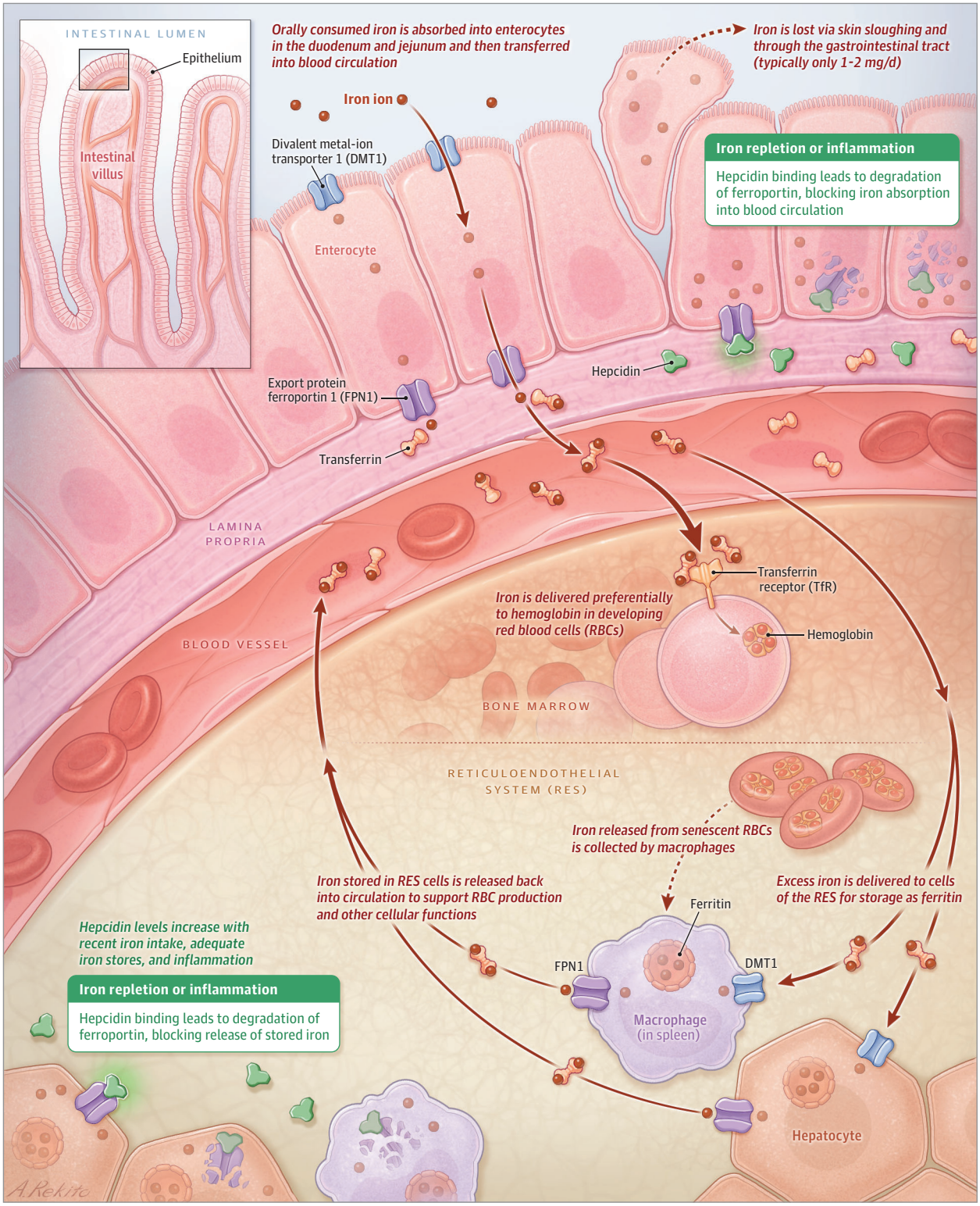
Pregnancy increases iron requirements by 1000 to 1100 mg.[14] Iron deficiency is common among pregnant individuals. A retrospective study reported absolute iron deficiency (ferritin <30 ng/mL) in 53% of 26 469 pregnant individuals.[15] In 629 primiparous individuals from Ireland who had iron parameters measured longitudinally at 15, 20, and 33 weeks, iron deficiency (ferritin <30 ng/mL or soluble transferrin receptor >4.4 mg/L) was documented in 21%, 44%, and 84% of participants, respectively.[16]

Potential GI sources of blood loss include inflammatory bowel disease (IBD), colorectal or gastric cancer, duodenal or gastric ulcers, esophagitis, gastritis, and colonic vascular ectasia. A study of 1036 individuals with IBD reported 27% had iron deficiency and 14% had iron-deficiency anemia.[17] In 2000 outpatients with IBD, 43% had absolute iron deficiency and 12% had iron-deficiency anemia; in these patients, iron deficiency was more common in those with active IBD (71%) vs quiescent disease (24%).[18]

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Figure 1. Iron Absorption, Storage, and Conservation in the Body



Aspirin or other nonsteroidal anti-inflammatory drugs can cause iron deficiency due to GI blood loss (occult or overt).[19] Chronic proton pump inhibitor (PPI) use reduces iron absorption by increasing gastric pH (low pH is necessary for iron absorption). In a meta-analysis that included 14 case-control and cohort studies (76 089 patients taking a PPI), the relative risk of iron deficiency among people taking a PPI compared with controls not taking a PPI was 2.56 ($P < .001$).[20]

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Box 1. Causes of Iron Deficiency

Increased Blood Loss
- Menstruation
- Pregnancy and delivery
- Gastrointestinal cancer
- Gastritis
- Ulcers, including Cameron ulcers (linear ulcers associated with hiatal hernia)
- Inflammatory bowel disease
- Chronic use of aspirin or nonsteroidal anti-inflammatory drugs
- Regular blood donation
- Intense athletic activity
- Hereditary hemorrhagic telangiectasia or other cause of nasal or gastrointestinal arteriovenous malformation
- Hookworm or other parasites
- Meckel diverticulum
- Gross hematuria

Reduced Absorption
- *Helicobacter pylori* infection
- Autoimmune or atrophic gastritis
- Inflammatory bowel disease
- Bariatric surgical procedure
- Long-term use of a proton pump inhibitor
- Celiac disease
- Rare hereditary conditions, such as atransferrinemia and iron refractory iron-deficiency anemia

Chronic Inflammation
- Cancer
- Rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus)
- Inflammatory bowel disease
- Chronic kidney disease
- Heart failure
- Endocrine disease (hypothyroidism)

In some low-resource countries, intestinal parasites (*Strongyloides* species, other soil-transmitted helminths, and *Schistosoma* species) cause absolute iron deficiency due to GI blood loss. Depending on their geographic origin, 8% to 86% of refugees to North America have parasitic infections that may cause iron deficiency.[21]

Iron deficiency may also result from decreased absorption of dietary iron due to intestinal conditions, such as atrophic gastritis, celiac disease, or a bariatric surgical procedure. In a meta-analysis of high-quality observational studies and RCTs comparing individuals infected with *Helicobacter pylori* (which causes achlorhydria, ulcers, and gastritis) with uninfected people, infection was associated with a higher rate of iron-deficiency anemia (odds ratio [OR], 1.72 [95% CI, 1.23-2.42]; 14 studies) and iron deficiency without anemia (pooled OR, 1.33 [95% CI, 1.15-1.54]; 30 studies).[22]

Celiac disease can cause occult blood loss from intestinal inflammation, decreased iron absorption through intestinal villus atrophy, and inflammation-induced hepcidin upregulation.[23,24] In a study including 382 adults with celiac disease, 145 (46%) had iron-deficiency anemia.[25] A systematic review that included 2998 patients with iron-deficiency anemia reported 3.2% had celiac disease.[26]

Iron deficiency is common in chronic diseases, such as chronic kidney disease (CKD [24%-85%]), IBD (13%-90%), HF (37%-61%), and cancer (18%-82%).[5] Obesity is associated with decreased iron absorption because adipose tissue produces hepcidin and induces inflammation, which further stimulates hepcidin production.[27] Three studies of 582 patients referred for a bariatric surgical procedure reported absolute iron deficiency with or without anemia in 6% to 22% of patients vs 6% to 7% of patients in the general population.[28]

Bariatric surgical procedures (Roux-en-Y, biliopancreatic diversions) may further impair iron absorption by bypassing small intestinal absorptive surfaces.[29] In 58 premenopausal women who underwent sleeve gastrectomy (n = 26) or Roux-en-Y gastric bypass (n = 32), heme iron (meat-based) absorption (measured by ^{59}Fe absorption) decreased from 24% preprocedure to 6% postprocedure and nonheme (plant-based) iron absorption decreased from 11% preprocedure to 5% postprocedure.[30]

Even in the absence of known risk factors, iron deficiency is highly prevalent. In the cross-sectional 2017 to 2020 NHANES study of 8021 US adults, 11% (95% CI, 10%-11%) without anemia, HF, CKD, or current pregnancy had absolute iron deficiency.[2]

Signs and Symptoms of Absolute Iron Deficiency

Individuals with absolute iron deficiency with or without anemia can be asymptomatic or may have 1 or more of the following signs or symptoms: fatigue; decreased exercise tolerance; RLS; pica, including pagophagia (ice craving); depression; and decreased attention and concentration (brain fog). Symptoms are often more severe in individuals with iron-deficiency anemia compared with those who have iron deficiency without anemia.[31-34]

Pica, especially pagophagia, is common (up to 50%) in individuals with absolute iron deficiency.[33] In 987 consecutive patients with absolute iron deficiency and iron-deficiency anemia (mean hemoglobin, 10.4 g/dL), 40% had pagophagia, 40% had RLS, and 22% had both.[33]

Physical signs of iron deficiency may include tongue depapillation, cheilosis, koilonychia (spoon nails), and diffuse nonscarring scalp alopecia. With more severe deficiency, including iron-deficiency anemia, patients may have pallor, pale conjunctiva, and, with severe anemia, tachycardia or a cardiac flow murmur.

RLS, which causes unpleasant sensations, cramps, and a sensation of needing to move the legs,[35] is associated with decreased brain iron (measured by magnetic resonance imaging) and with absolute iron deficiency with or without anemia. Two studies (1248 individuals with absolute iron deficiency with or without anemia) reported RLS in 32% and 40% of participants, respectively.[33,36] Two studies that included 335 patients with RLS reported absolute iron deficiency in 25% and 42% of patients, respectively.[37,38] In a meta-analysis of 10 RCTs (455 patients with RLS with or without anemia), both oral iron (2 trials) and intravenous (IV) iron (8 trials) supplementation significantly reduced leg discomfort and sleep disturbance symptoms relative to placebo (International Restless Legs Syndrome [IRLS] score decreased by 3.55 points).[39]

Iron Deficiency in Pregnancy

Iron deficiency may be associated with adverse fetal, neonatal, and maternal outcomes. In a study from Sweden of 532 232 pregnancies, adjusted for socioeconomic status, genetic background, and

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pregnancy complications, children of mothers with anemia diagnosed prior to 30 weeks' gestation, compared with children of mothers without anemia prior to 30 weeks' gestation, had increased rates of autism spectrum disorders (4.9% vs 3.5%; OR, 1.44 [95% CI, 1.13-1.84]), attention deficit hyperactivity disorder (9.3% vs 7.1%; OR, 1.37 [95% CI, 1.14-1.64]), and intellectual disability (3.1% vs 1.1%; OR, 2.20 [95% CI, 1.61-3.01]).[40] In a study of 18 948 443 pregnancies in China, postpartum hemorrhage (PPH) occurred in 2.07% of participants with prepartum anemia vs 0.81% of participants without anemia; the risk of PPH correlated with the severity of anemia (adjusted odds ratio [aOR] for mild anemia, 1.45 [95% CI, 1.43-1.47]; aOR for moderate anemia, 3.53 [95% CI, 3.47-3.60]; aOR for severe anemia, 15.65 [95% CI, 15.10-16.22]).[41] In a study involving 515 270 pregnant individuals from Canada, 65 906 of whom had anemia, prepartum anemia was associated with increased need for blood transfusions (5.1 per 1000 among women without anemia; aOR for mild anemia, 2.45 [95% CI, 1.74-3.45]; aOR for moderate anemia, 21.3 [95% CI, 12.2-37.3]), longer hospital stays, and higher rates of preeclampsia, placenta previa, and cesarean delivery.[42] In 166 566 deliveries in the US, in univariable analysis, antenatal anemia was significantly associated with maternal death (0.04% vs 0.01%; $P < .001$), transfusion during labor (2.9% vs 1%; $P < .001$), postpartum transfusion (6.7% vs 3.7%; $P < .001$), and PPH (13.8% vs 6.9%; $P < .001$). With multivariable logistic regression, anemia remained independently associated with severe maternal morbidity (a composite of maternal death, eclampsia, thrombosis, transfusion, hysterectomy, and intensive care unit admission), with an aOR of 2.44 (95% CI, 1.86-2.23).[43] Although iron deficiency accounts for 75% of all anemias during pregnancy, the cause of anemia was not always identified in the above studies, and associations between iron-deficiency anemia and adverse pregnancy outcomes may not reflect causation.

Diagnosis

Testing for Iron Deficiency

All patients with symptoms of iron deficiency or with anemia (hemoglobin below the reference limit) or unexplained microcytosis (mean corpuscular volume [MCV] <80 fL) should undergo testing with ferritin and/or TSAT (**Figure 2**), along with complete blood cell count if not done previously.

Serum ferritin is the first-line initial test for iron deficiency because iron deficiency is the only cause of low ferritin.[44,45] Based on expert consensus, the ferritin level to define absolute iron deficiency is typically less than 30 ng/mL,[1,46] which has 98% specificity and 92% sensitivity for absent bone marrow iron stores,[47] the standard for absolute iron deficiency. The sensitivity of ferritin for diagnosing iron deficiency is reduced in inflammatory conditions (IBD, HF, CKD, cancer) because ferritin, which is an acute phase reactant, increases with inflammation. In patients with absolute iron deficiency and a concurrent inflammatory condition, ferritin levels rarely exceed 100 ng/mL.[44] International and professional society guidelines vary in ferritin cutoffs for different conditions and populations (IBD, CKD, RLS, individuals who are menstruating, adults 65 years or older); therefore, if concern for iron deficiency exists despite ferritin of greater than 50 ng/mL, TSAT should be measured.[11]

TSAT quantifies the percentage of transferrin that is saturated with iron, and low TSAT (<16%-20%) indicates lack of bioavailable, circulating iron. Low TSAT is helpful to diagnose iron deficiency in individuals with IBD, CKD, cancer, and HF, in whom serum ferritin levels may be elevated due to inflammation.[48,49] TSAT should not be tested within 5 to 9 hours of ingesting iron-containing foods, vitamins, or supplements because serum iron increases with recent iron ingestion; fasting is not required if these ingestions are avoided.

Reticulocytosis (reticulocyte count >100 000/microL) following iron therapy is considered diagnostic of iron deficiency because it demonstrates that previously low levels of iron limited RBC production. Absence of reticulocytosis within approximately 1 week after iron therapy suggests alternate or concomitant diagnoses other than iron deficiency. Bone marrow aspiration with iron staining is rarely required to diagnose iron deficiency.

Hemoglobin and MCV are poor surrogates for iron deficiency and inadequate for diagnosis because anemia and microcytosis are late-stage findings. In a study that included 345 pregnant individuals who had complete blood cell count and ferritin level data, hemoglobin less than 11 g/dL and MCV less than 80 fL each only had a sensitivity of 30% for diagnosing iron deficiency (ferritin <30 ng/mL) during the first trimester.[50] Of 1749 individuals diagnosed with iron deficiency during any trimester of pregnancy, 50.5% did not have anemia or microcytosis.[50]

Screening

Recommendations for routine screening of asymptomatic, nonanemic, at-risk individuals for iron deficiency vary by professional organization. The American Society of Hematology, which has not previously issued screening recommendations for iron deficiency, is currently developing a guideline on this topic. The European Hematology Association (EHA) recommends screening patients at risk for developing iron deficiency, including athletes; vegetarians; regular blood donors; individuals who are menstruating; adults older than 65 years; people with certain chronic diseases (HF, CKD) or impaired absorption (celiac disease, short bowel syndrome, post–bariatric surgical procedure); individuals with bleeding disorders (von Willebrand disease, hemophilia); patients taking anticoagulants, anti-inflammatory or antiplatelet drugs, or PPIs; those with chronic or parasitic infections (hookworm); and socioeconomically disadvantaged individuals.[11]

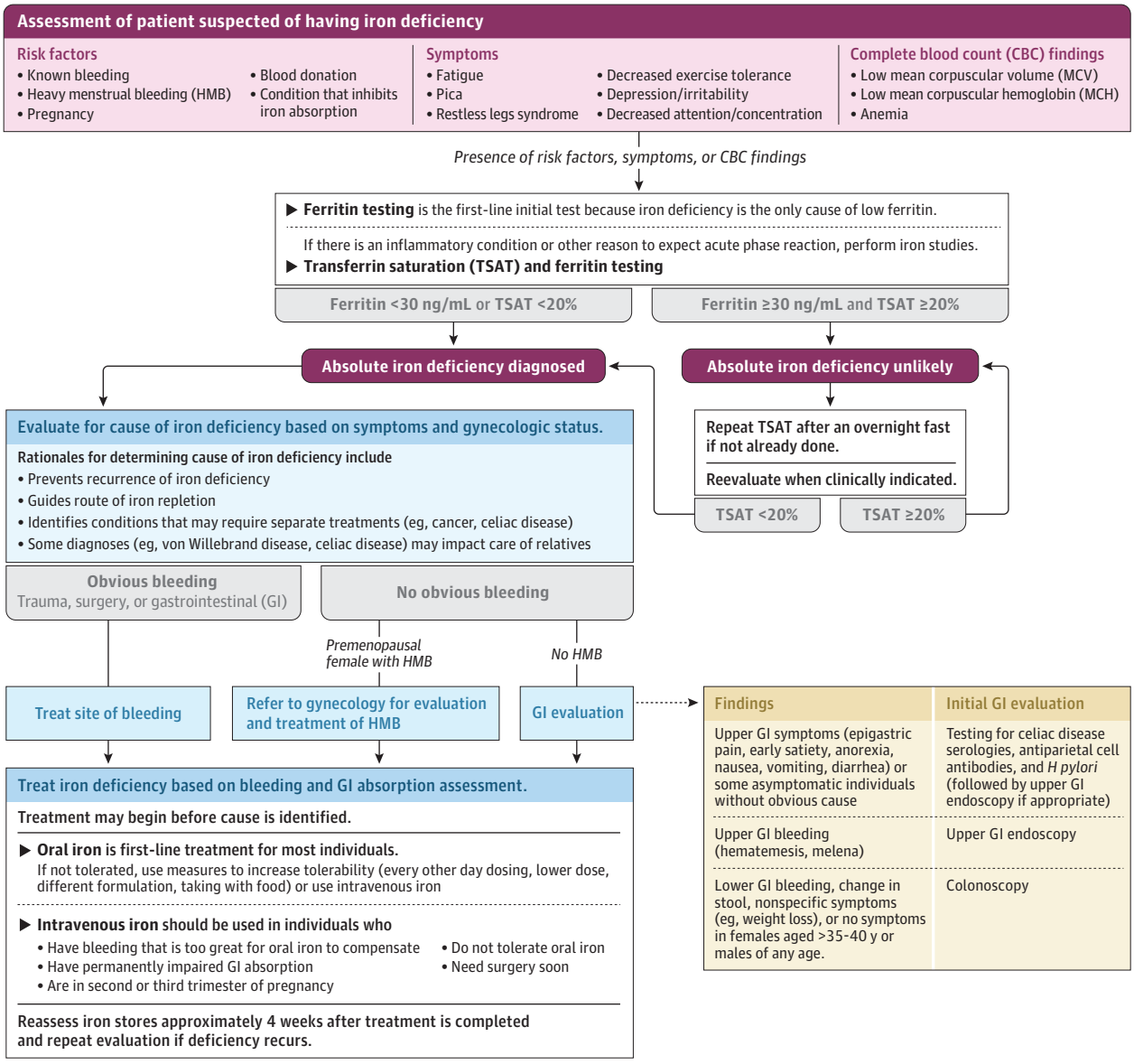
For pregnant individuals, guidelines on screening for iron deficiency vary. The 2024 US Preventive Services Task Force guideline found insufficient evidence to recommend for or against screening pregnant individuals for iron deficiency in the absence of anemia.[51] The American College of Obstetricians and Gynecologists recommends screening pregnant individuals for anemia and testing for iron deficiency only if anemia is present.[52] In contrast, the International Federation of Gynecology and Obstetrics and the EHA recommend screening all pregnant individuals and reproductive-age females for iron deficiency.[11,53]

Etiology of Iron Deficiency

The etiology of iron deficiency should be assessed in all patients (Figure 2). Heavy menstrual bleeding may be determined by the frequency of changing sanitary pads and/or tampons (>3/hour or during nighttime) and passage of clots (>1 in).[54] If menstrual bleeding is heavy, testing is indicated for anatomic lesions, such as uterine

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Figure 2. Evaluation and Treatment of Iron Deficiency



fibroids or polyps (ultrasound, hysteroscopy), and for bleeding disorders, such as von Willebrand disease.[11]

Inadequate dietary iron intake or malabsorption due to autoimmune gastritis or celiac disease can typically be identified by history and laboratory testing. Iron-poor diet, PPI use, or a bariatric surgical procedure can be determined from the history. For persons with iron deficiency and upper GI symptoms (dyspepsia, nausea, anorexia, epigastric pain), the American Gastroenterological Association (AGA) practice guidelines[45] recommend testing for *H pylori* and celiac disease.[55]

Patients with an uncertain cause of absolute iron deficiency after initial evaluation should typically undergo esophagogastroduodenoscopy and colonoscopy, even if asymptomatic.[45] An AGA technical review evaluating 18 studies (12 040 asymptomatic men and postmenopausal women with iron-deficiency anemia) reported that upper endoscopy detected upper GI cancer (gastric and esophageal) in 2.0% of patients and colonoscopy detected lower GI cancer in 8.9% of patients.[56] These rates were approximately 100-fold higher than those seen with general population screening. For patients with unrevealing initial endoscopies and no other causes of blood loss, capsule endoscopy can be considered, although supporting evidence is lacking.

Treatment

Oral iron is first-line treatment for most individuals with absolute iron deficiency (Figure 2). Oral iron preparations are widely available, inexpensive, and effective in treating absolute iron deficiency in most individuals when taken appropriately. A typical dose (ferrous sulfate, 325 mg) contains 60 mg of elemental iron and is taken once every other day or once daily. Treatment with oral iron should continue

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Box 2. Frequently Asked Questions About Iron Deficiency

Who should be tested for iron deficiency?

Testing for iron deficiency with a serum ferritin and/or transferrin saturation is appropriate for anyone with symptoms of iron deficiency (eg, fatigue, pica, restless legs syndrome), anemia, microcytosis, or risk factors such as ongoing blood loss from heavy menstrual bleeding, heart failure, chronic kidney disease, inflammatory bowel disease, cancer, or a bariatric surgical procedure. Guidelines vary about whether asymptomatic pregnant individuals should be screened for iron deficiency.

Which foods are high in iron, and can iron deficiency be treated by diet alone?

Adequate dietary iron is important for preventing iron deficiency, but after iron deficiency develops, the typical iron deficit of 1000 mg, plus daily needs of 1 to 5 mg, cannot be provided by diet alone. Foods highest in iron include animal meats, fortified cereals, and legumes (eg, lentils, chickpeas, beans [lima, soy, kidney, and white beans]).

How should oral iron be taken?

Oral iron can be taken once daily or every other day; compared with daily use, iron ingestion every other day has a similar efficacy and fewer adverse effects. Vitamin C may increase iron absorption, and calcium-containing foods, tea, and coffee consumed within 1 hour before and after taking oral iron may decrease iron absorption.

until ferritin, TSAT, and hemoglobin (in those with iron-deficiency anemia) return to the normal range. Use of enteric-coated and timed-release oral iron preparations reduces iron absorption, which may extend duration of therapy to 2 or more years.[57]

For patients with RLS who have a ferritin level less than 75 ng/mL and TSAT less than 45%, a 2018 guideline from the International Restless Legs Syndrome Study Group (IRLSSG) recommends daily use of oral ferrous sulfate with vitamin C for 12 weeks.[58]

Many individuals taking oral iron report nausea, constipation, diarrhea, metallic taste, and/or greenish-black stool.[59] A meta-analysis that included 20 RCTs with 3168 participants comparing ferrous sulfate with placebo showed that adverse effects were more common with oral iron than placebo (OR, 2.32; $P < .001$).[59] This meta-analysis also reported that adverse GI effects were more common with oral ferrous sulfate (doses ranging from 100 to 400 mg daily) than IV iron (OR, 3.05; $P < .001$), based on 23 RCTs with 3663 participants. In patients with IBD, oral iron reduced gut bacterial diversity.[60-63]

Alternate-day administration of equal doses of oral iron improves tolerance with similar efficacy. A masked, placebo-controlled RCT of 150 premenopausal women with absolute iron deficiency (ferritin ≤30 ng/mL) reported similar efficacy with oral iron taken daily for 90 days (serum ferritin, 43.8 ng/mL) and every other day for 180 days (serum ferritin, 44.8 ng/mL; $P = .98$), with significantly fewer GI adverse effects (nausea, stomach pain) in the alternate-day group (longitudinal prevalence ratio for GI adverse effects on days of iron intake, 1.56 [95% CI, 1.38-1.77]; $P < .001$).[64]

Increased dietary iron intake alone is insufficient to replete iron stores in patients with absolute iron deficiency (**Box 2**).[65,66] Fiber, calcium, coffee, and tea decrease oral iron absorption, so avoiding them within 1 hour before and after taking oral iron improves iron absorption. Iron absorption increases when oral iron is taken with vitamin C or meat protein.[12,67,68]

Monitoring and Follow-Up After Oral Iron

Adherence to oral iron therapy, adverse effects, and resolution of symptoms should be monitored because many individuals discontinue iron due to GI symptoms. Severity of iron deficiency informs the frequency of monitoring. Checking hemoglobin every 3 months during the first year after a diagnosis of iron deficiency and twice yearly during years 2 to 3 has been recommended by the EHA.[11] For iron-deficiency anemia, a minimum increase in hemoglobin of 1 g/dL is expected 2 weeks after starting oral iron.[69]

For oral iron intolerance, options include decreasing the dose and/or frequency, substituting a different formulation, or switching to IV iron (Figure 2).[69] If there is no increase in ferritin and/or TSAT and no increase in hemoglobin despite adherence to oral iron, evaluation is indicated for conditions such as autoimmune gastritis or celiac disease that impair iron absorption, and for ongoing GI blood loss or other causes of anemia.

IV Iron

Oral iron may not be adequate for treating iron deficiency or iron-deficiency anemia in individuals with heavy menstrual or chronic GI bleeding or those with impaired absorption. In these circumstances, IV iron should be first-line treatment (Figure 2). The eTable in the Supplement lists relevant clinical trials in these populations.

IV iron dosing, frequency, and duration depend on the cause of iron deficiency (Box 1). In the second and third trimesters of pregnancy, IV iron ensures sufficient iron delivery to the fetus for development.[70] Data suggest IV iron corrects anemia and fatigue faster than oral iron. In a randomized trial of 196 patients with postpartum iron-deficiency anemia, the median hemoglobin 6 weeks after therapy was 12.3 g/dL (95% CI, 10.6-13.8) with IV iron vs 11.7 g/dL (95% CI, 9.9-12.6) with oral iron.[71]

IV iron is first-line treatment for individuals with iron deficiency after a bariatric surgical procedure because these patients cannot adequately absorb oral iron.[72-74] For patients with IBD, IV iron causes fewer GI adverse effects than oral iron.[60-63] In inflammatory conditions, such as rheumatoid arthritis, CKD, IBD, cancer, and HF, oral iron may not be adequately absorbed, and IV iron may be necessary (Figure 1).[1,69,75,76]

IV iron is recommended by the 2018 IRLSSG guideline for patients with moderate to severe RLS who have a ferritin level less than 100 ng/mL and TSAT less than 45% who have a contraindication to oral iron, did not improve or did not tolerate oral iron, have a condition affecting oral iron absorption, or need a more rapid response than would be achieved with oral iron.[58]

There are no absolute contraindications to IV iron. However, IV iron is not recommended in the first trimester of pregnancy due to lack of safety data.

Comparison of IV Iron Formulations

In the US, 6 IV iron formulations are available: low molecular weight iron dextran, ferric gluconate, iron sucrose, ferumoxytol, ferric carboxymaltose (FCM), and ferric derisomaltose (FDI). Multiple studies have shown no difference in efficacy among these formulations. Low molecular weight iron dextran, ferumoxytol, FCM, and FDI can be administered in a single infusion over 15 to 60 minutes

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Table. Intravenous (IV) Iron Formulations

Agent	Low-molecular-weight iron dextran (INFeD [US]; CosmoFer [Europe])	Ferumoxytol (Feraheme)	Ferric carboxymaltose (Injectafer [US]; Ferinject [Europe])	Ferric derisomaltose (Monoferric [US]; Monofer [Europe])
Approved dosing	100 mg	510 mg	750 mg (US) 1000 mg (Europe)	1000 mg (20 mg/kg if <66 kg)
Optimal dosing	1000 mg over 60 min	1020 mg over 30 min	750 mg × 2 (US) 1000 mg (Europe) Both over 15 min	1000 mg over 20 min
Adverse events and special considerations[a]	Should not be confused with high molecular weight iron dextran no longer marketed	Inform radiologist if magnetic resonance imaging is performed within 8 wk of administration Exercise caution if substituting the generic formulation due to concerns about adverse events	May cause hypophosphatemia Avoid if serum phosphorus is low and monitor serum phosphorus in individuals receiving more than 1 infusion	Formerly known as iron isomaltoside

Refer to the eTable in the Supplement for representative clinical trials using these formulations.

[a] All formulations can cause infusion reactions that are not histamine mediated (frequency, 1%-4%). Anaphylaxis is possible with any medication, including IV iron, but true anaphylaxis with IV iron is exceedingly rare (<0.0005%).

(**Table**).[77,78] Iron sucrose and ferric gluconate require multiple IV infusions over several weeks.

Adverse Effects of IV Iron

IV iron does not typically cause GI adverse effects.[79] In a double-masked, double-dummy RCT of 96 patients with RLS, IV ferumoxytol and oral iron were similarly effective, decreasing IRLSS scores by 7.9 points with IV iron and 10.1 points with oral iron (P = .27).[80] The patients treated with IV ferumoxytol had fewer adverse events (55% with oral ferrous sulfate [mostly GI] vs 11% with ferumoxytol [mostly minor infusion reactions]).[80]

Use of IV FCM is associated with increased risk of hypophosphatemia, which can be prolonged and associated with symptoms of fatigue, cramps, and muscle weakness.[81] A randomized trial of 97 patients with IBD and iron-deficiency anemia reported hypophosphatemia in 8.3% of patients receiving FDI vs 51% of patients receiving FCM (adjusted risk difference, −42.8% [95% CI, −57.1% to −24.6%]; P < .001).[82] If more than 1 FCM infusion is given, serum phosphorous should be tested (on day 7, prior to the second infusion) and if hypophosphatemia is present, the second dose should be held.

Anaphylaxis occurs in approximately 1 of every 200 000 IV iron infusions, with no significant differences among formulations. A meta-analysis of 103 RCTs comparing IV iron (n = 10 390) with oral iron (n = 4044), placebo (n = 3335), and no iron (n = 1329) reported no increase in serious adverse events and no anaphylaxis with IV iron.[79]

Minor infusion reactions consisting of facial flushing, chest pressure, and back tightness can occur with IV iron; these reactions are not associated with wheezing, stridor, periorbital edema, or hemodynamic compromise. In 35 737 infusions (n = 12 237 patients), minor infusion reactions occurred in 1.4% to 4.3% of patients.[83] Premedication with diphenhydramine was associated with increased minor infusion reactions (38.6% with vs 1.7% without diphenhydramine).[83]

Infusion reactions are believed to be complement-mediated and resolve with stopping the infusion. This phenomenon has been called CARPA (complement activation–related pseudoallergy) or the Fishbane reaction.[84,85] Upon resolution, the infusion can be restarted at a slower rate, as CARPA reactions rarely recur. Infusion reactions should not be treated with epinephrine and diphenhydramine because these treatments are not effective and may be associated with adverse events, such as tachycardia and somnolence.

Monitoring After IV Iron

Hemoglobin, ferritin, and TSAT should be checked 4 weeks after IV iron infusion, and if they indicate insufficient repletion (ferritin <30 ng/mL; TSAT <20%), additional IV iron should be administered. Additional follow-up depends on the etiology of iron deficiency.

Transfusion

RBC transfusion should be reserved for patients requiring an immediate increase in hemoglobin, such as those with severe anemia (hemoglobin <7 g/dL) and life-threatening bleeding, cardiac ischemia, or hemodynamic instability due to anemia.[86] Although RBC transfusion treats anemia, it does not supply iron for erythropoiesis and does not adequately replete iron stores.

Limitations

This review has several limitations. First, it is not a systematic review, and the quality of included literature was not formally evaluated. Second, some relevant studies may have been missed. Third, some topics, such as functional iron deficiency, were not discussed.

Conclusions

Iron deficiency and iron-deficiency anemia are common conditions that may cause symptoms such as fatigue, exercise intolerance, and difficulty concentrating. Ferritin and/or TSAT are required for diagnosis and screening. The etiology of iron deficiency should be sought and treated. Oral iron is first-line therapy for most patients. IV iron is used for individuals who do not tolerate or have impaired absorption of oral iron, those with ongoing blood loss, certain chronic inflammatory conditions (IBD, CKD, HF, cancer), and during the second and third trimesters of pregnancy.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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