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Review Article

Iron Deficiency Anemia: Etiology, Pathophysiology, Diagnosis, and Treatment Approaches

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Abstract

Iron deficiency anemia (IDA) is a common health problem that affects about 1.24 billion people around the world, mostly children and women of childbearing age. IDA happens when the body doesn't get enough iron, loses too much iron, or can't absorb it properly. This makes erythropoiesis, cellular metabolism, and immune function worse. The World Health Organization says that 40% of women who are pregnant and 32.5% of women who are not pregnant have anemia. People with IDA often feel tired, weak, pale, and have trouble thinking clearly. Lab tests, such as hemoglobin, blood ferritin, and transferrin saturation, are used to make the diagnosis. You can treat the condition in two ways: by taking iron supplements by mouth, such as ferrous sulfate, ferrous gluconate, and ferrous fumarate; or, for serious cases, by giving iron through an IV. Strategies for prevention depend on increasing the amount of iron you get from food, making it more bioavailable, and keeping infections under control. Food addition and fortification programs have been shown to help lower the number of people with IDA. However, problems still exist, especially in areas with poor economies. Recent advance in acknowledging how iron is used and controlled has implications for creating targeted therapeutic approaches. A key regulator of iron balance, hepcidin, is a key player in the pathophysiology of IDA. This review shows how complicated IDA is and how important it is to have treatment plans that consider underlying causes, dietary factors, and socioeconomic factors.

Keywords: Iron Deficiency Anemia (IDA), Erythropoiesis, Hemoglobin, Nutritional Deficiencies, Neurological Disorders, Iron Supplements.

Introduction:

Anemia is a significant health problem.[1] Iron is a crucial element of hemoglobin (Hb) and is required for other metabolic activities, distinct from its involvement in erythropoiesis.[2] Approximately 1.24 billion individuals globally are afflicted by iron deficiency anemia (IDA).[3] Iron deficiency accounts for fifty percent of all anemia cases.[4] Iron deficiency anemia (IDA) is a serious condition that impacts young children and women of reproductive age in economically weak nations.[5] The causes of iron deficiency may result from excessive loss or, less commonly, reduced absorption.[6] The World Health Organization estimates that 40% of pregnant women suffer from anemia.[7] Iron deficiency adversely impacts erythrocyte production and disrupts cellular activities associated with muscle metabolism, as well as impairing mitochondrial function, neurotransmitter activity, DNA synthesis, and immune system activity.[4] The World Health Organization (WHO) identifies iron deficiency as the most prevalent dietary deficit, impacting 1.62 billion individuals, with a peak prevalence of 47.4% among preschool children [WHO, 2001].[8] Anemia may arise from several etiologies, including nutrition-related deficiencies, infections, inflammatory diseases, acute or chronic hemorrhage, and hereditary hemoglobin abnormalities.[9]

Table 1: Global Prevalence of Iron Deficiency and Anemia:[10]

Iron deficiency	Prevalence
Children (under 2 years)	9.0
Children aged 3 to 5 years	4.5
Adolescent females (ages 12–19)	15.6
Females aged 20 to 49 years	15.7
Women of childbearing (15–49 years) who are pregnant	18.0
in the general population	12.2
Hospitalized population	23.0
Anaemia in the general population	32.9
Preschool children (0–5 years)	43.0
Children of school (over 5 years)	25.4
Non-pregnant women (15-49 years)	29.0
Adolescent pregnant women (15–19 years)	38.0
Men aged 15 to 60 years	12.7
Individuals aged beyond 60 years	23.9

Iron deficiency anemia (IDA) can be detected by markers including hemoglobin, serum ferritin, transferrin receptors, transferrin saturation/total iron binding capacity, and zinc protoporphyrin.[11]

Iron metabolism:

Iron is a crucial element in several enzymes which promote various metabolic processes, including deoxyribonucleic acid (DNA) replication and repair, adenosine triphosphate (ATP) synthesis, oxygen transport, and electron transport, required for the proper functioning of all body cells.[12] Alterations or anomalies in the regulatory systems can affect the rate of iron absorption and the total body iron concentration. Increased iron absorption is seen in genetic disorders including hereditary haemochromatosis and thalassaemia intermedia, resulting in iron overload in both situations.[13] In the processes of iron absorption and distribution, it is strongly linked to proteins (transferrin), resulting in an exceedingly low quantity of free intracellular iron.[14]

Approximately 75% of iron is associated with heme proteins, specifically hemoglobin (the predominant iron-containing protein) and myoglobin.[12] A daily consumption of 15 - 20 mg of iron results in an absorption of just 1 - 2 mg/day in the duodenum and the first segment of the jejunum. There are two types of iron that are absorbed, namely. Haem (10%) and non-haem (90% ionic).[15] Heme and non-heme iron are the two primary dietary sources of iron.[12]

In the enterocyte, a little quantity of iron is stored as ferritin, while the remainder is conveyed over the basolateral membrane into the circulation by the Fe2+ transporter ferroportin 1 (Ireg-1), facilitated by the protein hephaestin, which converts Fe2+ to Fe3+. Consequently, iron that enters the circulation is absorbed by transferrin, which preserves Fe3+ in a redox-inert condition and transports it to tissues. A considerable amount of this iron is also stored in macrophages as ferritin.[15]

The absorption percentage of iron from a cow milk formula reduces with increasing iron concentration; approximately 6% is absorbed from a formula with 6 mg of elemental iron/L, whereas about 4% is absorbed from a formula with 12 mg of elemental iron/L.[12] Hepcidin is a key regulator of iron, modulated by iron demand, iron reserves, erythropoiesis, hypoxia, and inflammation. It is mostly generated in the liver and released into the circulation.[16]

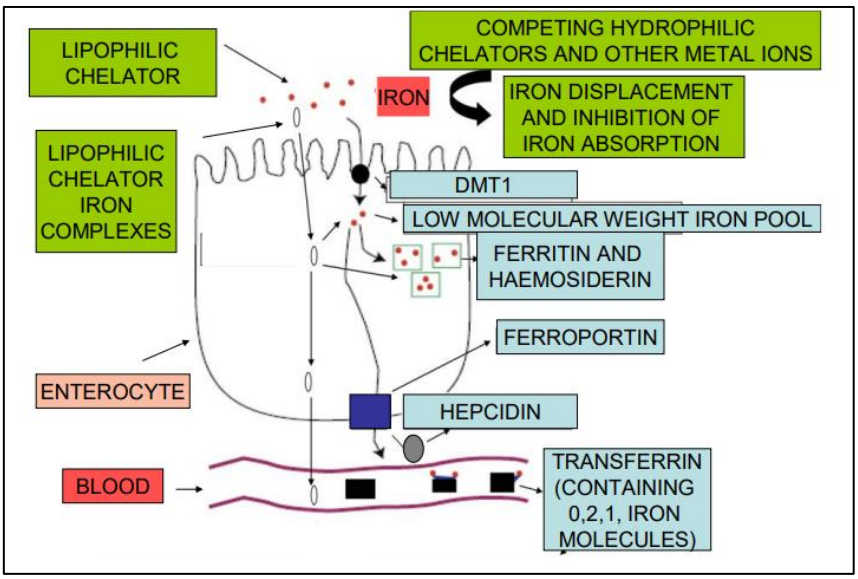

Figure 1: Mechanism of iron absorption at the enterocyte.[13]

Signs and symptoms of iron deficiency anemia:

Iron deficiency (ID) may be asymptomatic; however, it can also lead to significant symptoms in some individuals. Symptoms associated with iron deficiency include fatigue, irritability, dyspnea, headache, hair loss, impaired concentration, pica, restless legs syndrome, and alterations in epithelial cells, including dry mouth, cheilitis, atrophic glossitis, Plummer-Vinson pharyngeal webs, and reduced physical performance.[17,18] Clinical signs and symptoms of iron deficiency anemia are limited and frequently unrecognized.[18]

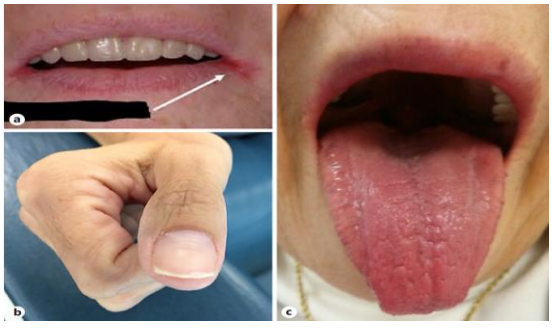

Figure 2: a) Angular cheilosis characterized by fissures at the corners of the mouth. b) Examples of physiological indicators of iron shortage. c) Horizontal lines on the fingernails (Mees lines). Depapillation of the tongue.[19]

Etiology of iron deficiency anemia:

The cause of iron deficiency anemia is quite variable.[12] Iron deficiency (ID) and subsequent iron deficiency anemia (IDA) can arise from several physiological, environmental, pathological, and hereditary factors (Fig. 3).[20] Iron deficiency, with or without anemia, may be either independent or due to an underlying illness, or may arise in the setting of numerous clinical conditions (e.g., in the elderly). Iron deficiency is often acquired and seldom inherited.[21] The organic physiological loss of iron transpires through bile, urine, and the desquamation of skin and intestinal lining.[22]

Reduced absorption is recognized in specific dietary patterns, with many inhibitors of iron absorption identified, including calcium, phytates (found in grains), and tannins (found in tea and coffee).[20] The prevalence of folate and vitamin B12 deficiencies is increasing. This may be attributable to dietary factors and inadequate absorption, such as post-gastric bypass surgery.[10] Iron shortage may result from a sustained consumption of iron-deficient foods, increased iron demands (such as during pregnancy and breastfeeding), blood loss, or gastrointestinal loss of iron.[23] The predominant cause of iron deficiency anemia (IDA) during pregnancy is dietary inadequacy coupled with insufficient initial iron reserves that fail to meet the increasing iron requirements.[24]

A difference between the maximum dietary iron absorption and physiological needs during periods of increased demand results in anemia.[19]

In term newborns, due to the ample iron reserves at birth, iron deficiency anemia is rare before to 6 months of age. Preterm newborns, as well as twins, triplets, and quadruplets, exhibit low iron reserves at delivery.[12] Infantile risk factors encompass (a) dietary elements, including prolonged exclusive breastfeeding without timely introduction of iron-rich complementary foods, utilization of low-iron infant formula, administration of unmodified cow's milk, goat's milk, or soy milk, inadequate provision of iron-rich complementary foods, and excessive consumption of cow's milk; and (b) non-dietary elements, such as recurrent respiratory tract infections, chronic infections like malaria and HIV, gastrointestinal malabsorptive disorders including celiac disease, chronic intestinal infections or infestations, conditions causing gastrointestinal blood loss such as milk protein-induced enterocolitis, hookworm infestation, and inflammatory bowel disease.[9]

In children, loss also occurs due to the presence of blood in the stools and the consumption of liquid whole milk during the first year of life.[22] Children in underdeveloped countries are especially susceptible to iron deficiency due to their growth requirements, diets with low iron bioavailability, and significant helminthic infestations.[14] The primary signs of this illness are pallor, glossitis, and the patient may report lassitude, weakness, anorexia, palpitations, and dyspnea.[25]

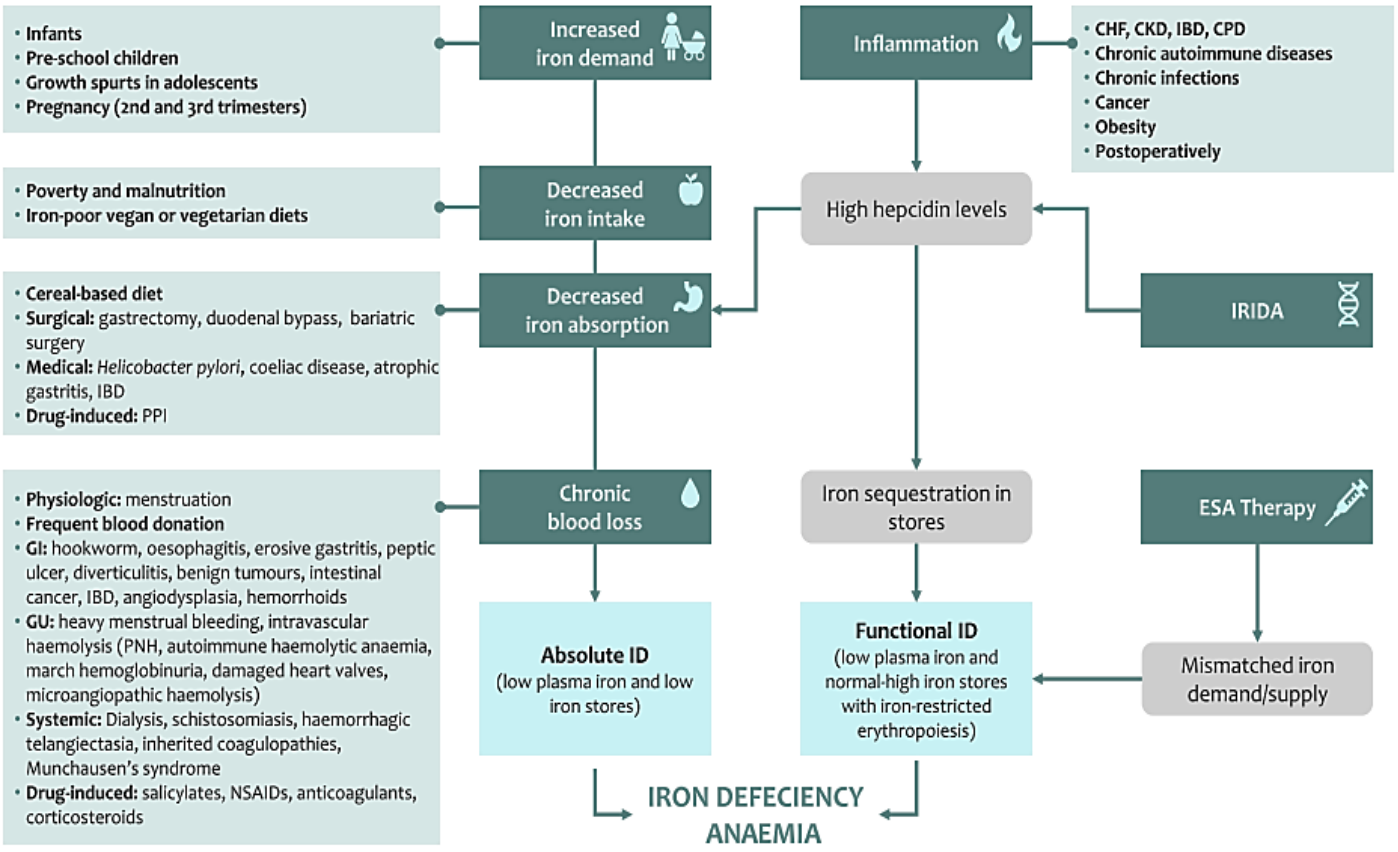

Figure 3: Diverse Etiology of iron deficient anemia.[20]

Epidemiology of iron deficiency anaemia:

The prevalence of anemia caused by iron deficiency is influenced by several factors, including age, dietary habits, socioeconomic level, ethnic composition, and diagnostic criteria.[12] In 2016, 41.7% of children under five years, 40.1% of pregnant women, and 32.5% of non-pregnant women were globally affected by anaemia.[26] Prevalence rates differ by nation; it impacts 2.4 million children in the USA, 5.4% of children in Spain, 14.0% in Estonia, and 30.8% in Brazilian youngsters.[19]

The World Health Organization defines anemia as haemoglobin (Hb) values below 13 g/dL in males and below 12 g/dL in nonpregnant women.[27] The WHO estimates that 42% of anemia cases in children and 50% in women can be treated via iron supplementation, with regional variations.[26] Globally, there are more than 1.2 billion instances of iron deficiency anemia, and iron deficiency without anemia may be even more widespread.[28] In 2017, the Global Burden of Diseases Study indicated that dietary iron deficiency ranks as the fourth and twelfth largest cause of years lived with disability in women and men, respectively.[29]

The epidemiological data on iron deficiency anemia are unreliable, particularly as anemia is frequently attributed to iron deficiency regardless of its underlying etiology. The WHO believes that 50% of global cases are attributable to iron deficiency; nevertheless, there are regional and subgroup inequalities. In two investigations conducted during the previous three years, the prevalence of iron deficiency anemia was around 20%.[30]

The pathophysiology of iron deficiency anemia:

Iron is a crucial element regulated mainly by dietary consumption, intestinal absorption, and iron recycling.[31] In Western countries, other healthy persons may be susceptible. This includes vegetarians, particularly vegans, due to dietary restrictions, as well as blood donors.[21] In these nations, the primary cause of iron deficiency anemia (IDA) is not the inadequate iron content of the diet, but rather the low bioavailability of iron, as it is derived from plant sources that are high in iron absorption inhibitors.[32] Anemia is linked to adverse health and developmental consequences, such as neonatal and perinatal death, low birth weight, early birth, and delayed child development.[33] Iron loss significantly impacts iron homeostasis, triggering adaptive processes in the hepcidin-ferroportin (FPN) axis, the iron regulatory protein (IRP)/iron responsive element (IRE) system, and other regulators.[18]

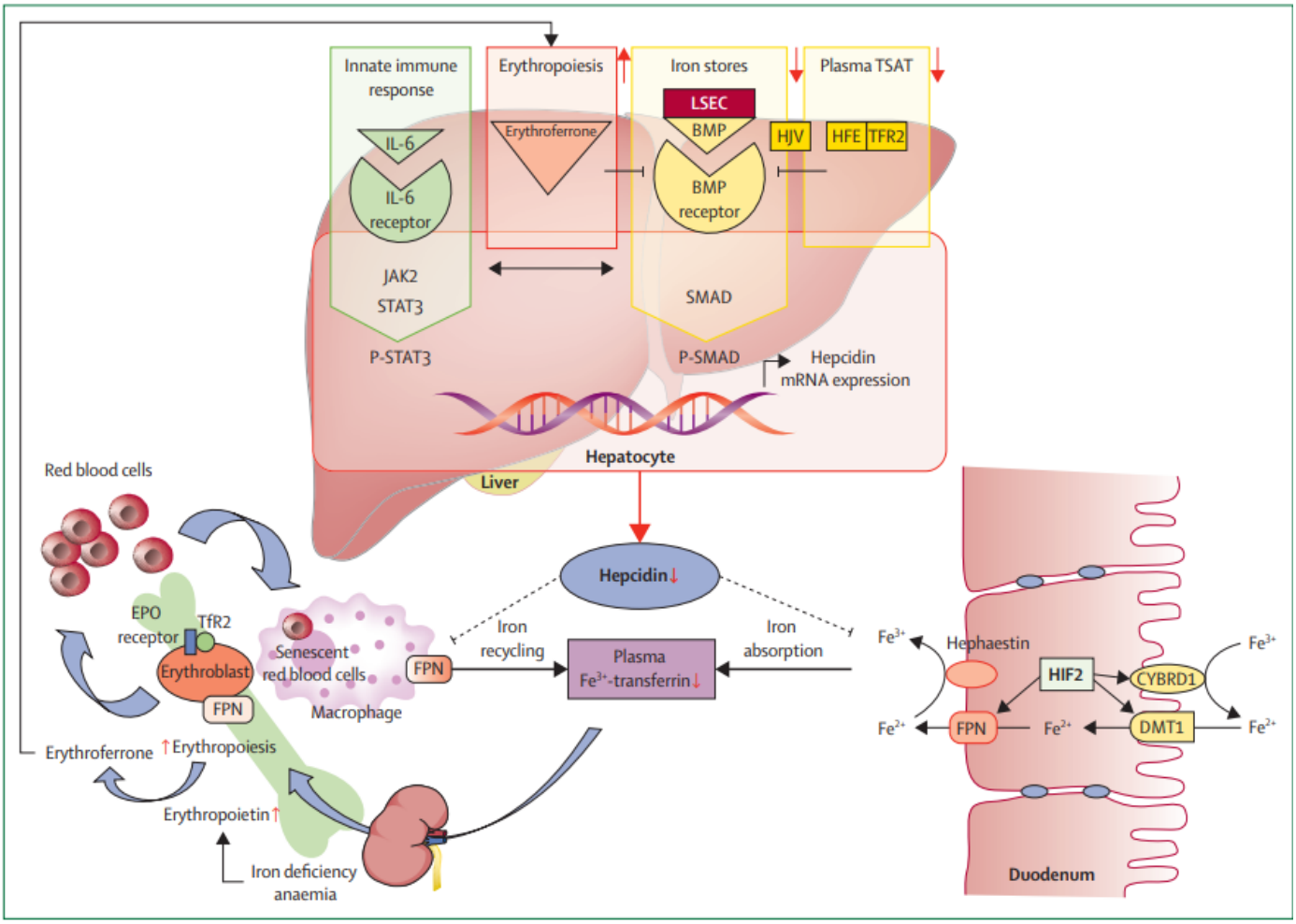

Figure 4: Pathophysiology and homeostatic response to iron deficiency.[26]

Heme iron is readily absorbable and originates from hemoglobin (Hb) and myoglobin found in animal flesh, poultry, and fish.[31] The objective is to enhance iron use through erythropoiesis and to mitigate the physiological suppression of iron absorption.[18] The adverse health and developmental consequences of anemia result from reduced oxygen transport to tissues, potentially impacting several organ systems, with complications associated with the underlying causes of anemia, which are challenging to differentiate. In iron deficiency anemia (IDA), reduced iron availability has recognized negative effects on brain development and function even before the onset of anemia.[33]

The clinical implications of iron deficiency extend beyond erythropoiesis, as iron is a crucial component in enzymes associated with cellular respiration, oxidative phosphorylation, the citric acid cycle, nitric oxide synthesis, and the creation of oxygen radicals. Metabolically active cells, including cardiac and skeletal muscle cells, need on iron for their functional and structural integrity.[34]

The body necessitates around 25 mg of iron day, mostly utilized for the synthesis of hemoglobin in erythrocytes.[20] Hepcidin levels rise during the first trimester of pregnancy compared to non-pregnant states, thereafter, decreasing in the second and third trimesters.[35] The condition impacts between 4% to 15% of the general population, encompassing children and adolescents.[36]

Systemic iron homeostasis in health is regulated by the peptide hormone hepcidin, synthesized in the liver.[10] A significant increase in plasma volume is usually indicated by a reduction in hemoglobin (Hgb) levels.[17]

Diagnosis and prevention of iron deficiency anemia:

Anemia is characterized by the World Health Organization (WHO) guidelines as hemoglobin levels below 130 g/L in males and below 120 g/L in women. Mild anaemia is classified as hemoglobin levels equal to or more than 110 g/L, moderate anaemia as levels below 110 g/L, and severe anaemia as levels below 80 g/L. AI often manifests as mild to moderate normocytic, normochromic anemia characterized by diminished circulating iron concentrations, normal or elevated ferritin levels, and reduced transferrin levels.[37]

To diagnose iron deficiency anemia, we can use a step-by-step approach. this start by checking for microcytosis, a condition where red blood cells are smaller than normal. We then use a combination of blood tests, including serum ferritin levels (SF) and transferrin saturation (TST), to confirm the diagnosis. We also carefully review the patient's medical history.

When evaluating a patient with a specific type of anemia, we first check for a genetic disorder called β-thalassemia, especially in people from areas where this disorder is common.[38]

Hepcidin, a protein that helps regulate iron levels, is not reliable on its own to diagnose patients with complex cases of iron deficiency. This is because hepcidin levels can fluctuate in these patients, making it difficult to distinguish them from those with normal iron levels or iron deficiency.

To address this challenge, researchers evaluated the effectiveness of a test called RetHe in identifying patients with complex cases of iron deficiency. The results showed that RetHe can accurately predict which patients are likely to respond to iron treatment. Based on this study, a RetHe cutoff point of less than 30 pg was established for diagnosing iron deficiency anemia.[39]

It is essential to regularly check hemoglobin and iron levels in all patients to ensure accurate diagnosis and treatment. .[40]

An accurate diagnosis necessitates laboratory examinations. Reduced serum ferritin levels signify absolute iron deficiency, indicating exhausted reserves. Levels of 30 mg/L are the recognized threshold for identifying moderate instances; in the presence of anemia, ferritin levels are often lower, ranging from 10 to 12 mg/L. In the absence of inflammation or illness, serum ferritin exhibits the most significant connection with bone marrow stainable iron, which was considered the gold standard for evaluating iron reserve depletion.[18]

In children aged 6 to 59 months, a hemoglobin concentration below 11 g/dL signifies anemia. To ascertain if anaemia is attributable to iron deficiency, it is essential to evaluate supplementary indicators of iron status, including reticulocyte hemoglobin, serum ferritin, serum transferrin receptor, total iron binding capacity, transferrin saturation, zinc protoporphyrin concentration, and erythrocyte protoporphyrin concentration. Reticulocyte hemoglobin serves as a clinically valuable indicator for assessing iron deficit and hematological responses during iron therapy, emerging as a potential biomarker to replace biochemical iron tests in diagnosing iron deficiency anemia.[9]

The effect of iron deficiency on the central nervous system (CNS) is very significant. Iron is essential for the proliferation, differentiation, myelination, and dopamine neurotransmission of brain cells.[19] Laboratory assessment is essential for an accurate diagnosis of iron insufficiency and iron deficiency anemia (IDA). The etiology of anemia encompasses several factors; hence diagnosis cannot rely just on hemoglobin measurements. To achieve diagnostic clarity, it is essential to assess red blood cell count and serum ferritin levels. The most dependable indicator of deficiencies in iron is serum ferritin (SF), and it is advisable to test SF concentration at the onset of pregnancy.[41]

Ultimately, people with a ferritin concentration within the normal range may yet possess inadequate iron reserves that fail to satisfy their anticipated iron requirements. This may apply to pregnant women, blood donors with ferritin levels below 50 ng/mL, or those scheduled for surgical operations expected to involve moderate to severe blood loss, with ferritin levels below 100 ng/ml.[42]

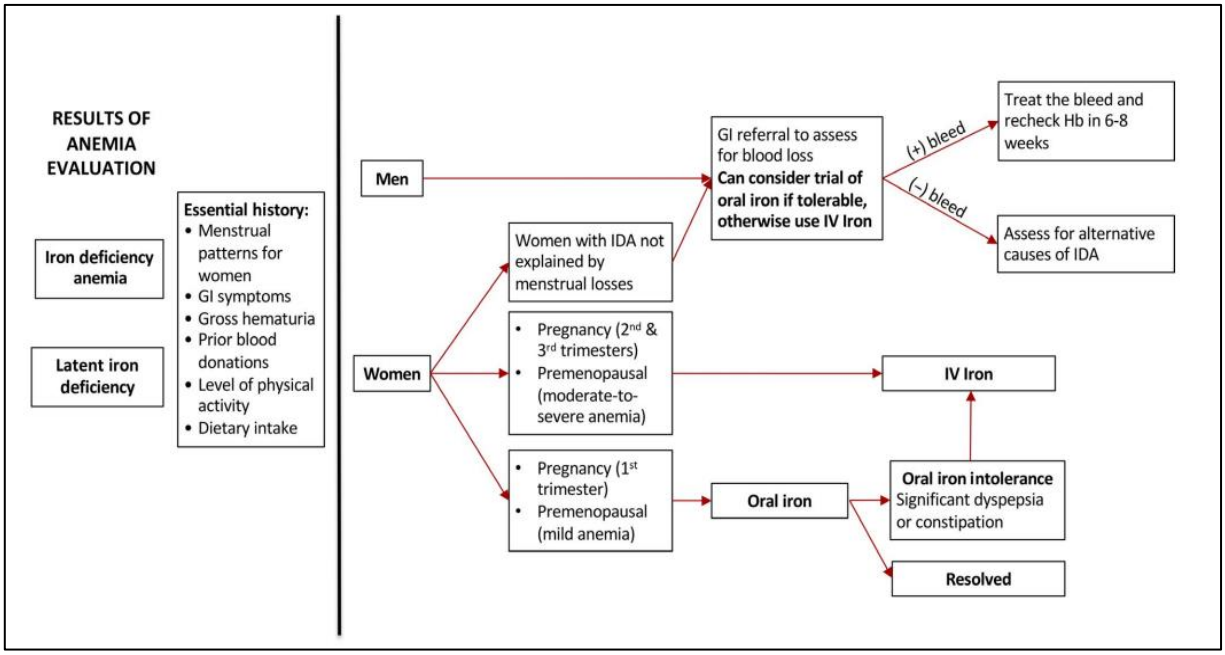

Figure 5: Diagnosis and prevention of iron deficiency anemia in adults.[43]

Prevention of iron deficient anemia:

Iron supplementation is indicated in two primary conditions: to avoid iron-deficiency anemia in at-risk groups or to treat persons exhibiting symptoms and laboratory-confirmed iron deficiency.[10]

As mentioned earlier, anemia affects the health of both the mother and the child; thus, its prevention and treatment are important.[44]

Management of iron deficiency anemia:[45]

a. Improve participation via education and periodic iron supplementation.

b. Infection control is crucial in the endemic environment.

c. Properly diagnosing the underlying causes of anemia.

d. Collaborative partnership.

e. A pilot area for the project is necessary for expanded coverage.

f. Enhancing the diversity of eaten fortified foods and monitoring iron excess.

Treatment for iron deficiency anemia:

The selection of the appropriate treatment for anemia is based upon its etiology and severity. Factors such as the duration till birth, the degree of anemia, additional risks, maternal complications, and patient preferences are crucial in determining the treatment method.[41] Although iron shortage is widespread, the success rate of readily available oral iron therapies is often inadequate, leading to frequent adverse effects. This is partially due to the characteristics of the human iron regulatory system, which prioritizes the long-term avoidance of iron excess and restricts the fast correction of iron shortage by oral treatment.[46]

Food items are a primary source of dietary iron, and its bioavailability is highly dependent upon its chemical structure, nutritional characteristics, and concentration. In recent years, the increasing prevalence of individuals impacted by this micronutrient shortfall has spurred the advancement of non-therapeutic methods designed to reduce iron deficiency in the human body. Alongside the intake of iron-rich meals, (bio)fortification strategies encompass many methods designed to mitigate the deficiency of this element and its associated effects, enhancing its bioavailability for absorption by the human body.[47]

1. Oral iron formulations:

Preparations delivering a higher amount of elemental iron per dosage should be the preferred option. In addition to the elemental iron level, the adverse effects of these preparations, such as nausea, vomiting, and stomach discomfort, must also be taken into account.[15] When food sources are inadequate for restoring maternal iron reserves, typical oral formulations of iron supplements (ferrous sulfate, ferrous gluconate, and ferrous fumarate) are accessible at most pharmacies (table no. 2).[48]

Ferrous sulfate comprises 20% elemental iron per pill. Ferrous salts include ferrous gluconate (12% elemental iron), ferrous fumarate (33% elemental iron), ferrous succinate (35% elemental iron), and iron polymaltose (28% elemental iron).[18]

The most prevalent adverse effects encompass nausea, epigastric discomfort, diarrhea, constipation, and black stool staining, all of which frequently result in inadequate adherence.[49]

Iron, as a heavy metal, readily forms salts upon interaction with diverse anions, and several such compounds are utilized for medicinal purposes. Numerous oral iron formulations exist for the management of iron deficiency anemia (IDA), although ferrous sulfate (F.S.) is the primary oral iron product utilized globally.[32]

Table 2: Common Oral Iron Supplements:[48]

Generic drug	Brand name	Elemental iron content	Cost	Adverse gastrointestinal effect
Ferrous sulfate	Feosol (tablet) Ferro-Bob, FerrouSol (tablet) FeroSul (liquid) Fer-In-Sol (drops)	65 mg 65 mg 44 mg/5mL 15 mg/1mL	Inexpensive and readily available	Increased
Ferrous fumarate	Ferrimin 150 (tablet) Ferretts, Ferrocite, Hemocyte (tablet) Various over-the-counter products with "iron" in the name	150 mg 106-325 mg 29.5-90 mg	Expensive	Less
Ferrous gluconate	Fergon, Ferrotabs (tablets)	27 mg	Expensive	Less
Ferric maltol	Accufer (capsules)	30 mg	Expensive	Improved tolerance
Polysaccharide-iron complexb 125	NovaFerrum/ NovaFerrum 125 Ferrex 150 (capsules)	15 mg/1 mL (drops) / 125 mg/5 mL (liquid) Elemental iron varies by product	Multiple formulations	Poorly studied in pregnancy

2. Parenteral iron formulations:

Iron is delivered intravenously as complexes of iron carbohydrates, which consist of a mineral core made of polynuclear iron (III)-hydroxide coated in a carbohydrate ligand.[15] Recent formulations, including low-molecular-weight iron dextran and ferric carboxymaltose (Injectafer), are accessible and exhibit less documented adverse responses.[48] Once limited by the risk of severe hypersensitivity reactions, this route of administration is currently more widely used as a result of the improved safety profile of last generation compounds.[18]

The formulations in use (Table 3) include colloids consisting of elemental iron encased in a carbohydrate shell.[18] Intravenous iron has demonstrated superior efficacy compared to oral iron in the treatment of iron deficiency anemia and is typically more tolerated; nevertheless, universal delivery is constrained by availability and expense.[49]

Intravenous iron entirely overcomes the intestinal hepcidin-ferroportin mechanism that governs iron absorption; yet, its utilization in children with iron deficiency anemia is rare due to its elevated cost and the scarcity of pediatric research supporting its safety and efficacy.[32]

Table 3: Primary intravenous iron formulations accessible.[18]

Formulations	Dosage	frequency
Iron sucrose	200 mg	5 doses over 2 weeks
Ferumoxytol	510 mg	2 doses, 3-8 days apart
Ferric gluconate in sucrose complex	250 mg	4 doses weekly
Ferric carboxymaltose	750 mg	2 doses, 1 week apart
Iron isomaltoside	1000 mg	1 dose
Iron dextran (low molecular weight)	500 to 1000 mg	variable

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References

1. Kaur T, Upadhyay J, Nandave M, Alsayari A, Alshehri SA, Pukale S, Wahab S, Ahmad W, Rashid S, Ansari MN. Exploring progress in iron supplement formulation approaches for treating iron deficiency anemia through bibliometric and thematic analysis. Heliyon. 2024 Apr 4;10(7):e29058. https://doi.org/10.1016/j.heliyon.2024.e29058 PMid:38623202 PMCid:PMC11016621

2. Khoury A, Pagan KA, Farland MZ. Ferric Maltol: A New Oral Iron Formulation for the Treatment of Iron Deficiency in Adults. Ann Pharmacother. 2021 Feb;55(2):222-229. https://doi.org/10.1177/1060028020941014 PMid:32633548

3. Benson CS, Shah A, Frice MC, Frice CJ, "Iron deficiency anaemia in pregnancy: A contemperory review, Obsteric Medicine", 2021;14(2):67-76. https://doi.org/10.1177/1753495X20932426 PMid:34394714 PMCid:PMC8358243

4. Kurbonova GA, Lapasova ZK, "Current Views on Iron Deficiency Anaemia In Patients With Cardiovascular Disease", 2022; 4(3): 59-64. https://doi.org/10.37547/TAJMSPR/Volume04Issue03-12

5. Hussain U, Zia K, Iqbal R, Saeed M, Ashraf N. Efficacy of a Novel Food Supplement (Ferfer®) Containing Microencapsulated Iron in Liposomal Form in Female Iron Deficiency Anemia. Cureus. 2019 May 7;11(5):e4603. https://doi.org/10.7759/cureus.4603

6. Kumar A, Gupta S, Meena LP, Meher MP, Rai M, Kumar S, Bharti A. Study to evaluate the etiology of iron deficiency anemia at a teaching hospital in northeastern part of India. J Family Med Prim Care. 2020 Jun 30;9(6):3076-3081. https://doi.org/10.4103/jfmpc.jfmpc_3_20 PMid:32984176 PMCid:PMC7491828

7. Gupte S, Mukhopadhyay A, Puri M, Gopinath PM, Wani R, Sharma JB, Swami OC. A meta-analysis of ferric carboxymaltose versus other intravenous iron preparations for the management of iron deficiency anemia during pregnancy. Rev Bras Ginecol Obstet. 2024 Mar 15;46:e-rbgo21. https://doi.org/10.61622/rbgo/2024AO21 PMid:38765534 PMCid:PMC11075392

8. Burton JK, Yates LC, Whyte L, Fitzsimons E, Stott DJ. New horizons in iron deficiency anaemia in older adults. Age Ageing. 2020 Apr 27;49(3):309-318. https://doi.org/10.1093/ageing/afz199 PMid:32103233

9. Sundararajan S, Rabe H. Prevention of iron deficiency anemia in infants and toddlers. Pediatr Res. 2021 Jan;89(1):63-73. https://doi.org/10.1038/s41390-020-0907-5 PMid:32330927

10. Benson CS, Shah A, Stanworth SJ, Frise CJ, Spiby H, Lax SJ, Murray J, Klein AA, "The effect of iron deficiency and anaemia on women's health", Association of anaesthetics, 2021; 76(4): 1-2. https://doi.org/10.1111/anae.15405 PMid:33682105

12. Wiafe MA, Ayenu J, Eli-Cophie D. A Review of the Risk Factors for Iron Deficiency Anaemia among Adolescents in Developing Countries. Anemia. 2023 Jan 3;2023:6406286. https://doi.org/10.1155/2023/6406286 PMid:36636253 PMCid:PMC9831712

13. Leung, A. K. C., Lam, J. M., Wong, A. H. C., Hon, K. L., Li, X., Iron deficiency anameia: an updated review, Current pediatric reviews, 202420(3), 1-3. https://doi.org/10.2174/1573396320666230727102042 PMid:37497686

13. Kontoghiorghes GJ, Kolnagou A, Theodora D, Neocleous M, Kontoghiorghe CN, "New Era in the Treatment of Iron Deficiency Anaemia Using Trimaltol Iron and Other Lipophilic Iron Chelator Complexes: Historical Perspectives of Discovery and Future Applications" International journal for molecular science ,2021; 22(5546): 1-34. https://doi.org/10.3390/ijms22115546 PMid:34074010 PMCid:PMC8197347

14. Animasahun BA, Itiola AY, "Iron deficiency and iron deficiency anaemia in children: physiology, epidemiology, aetiology, clinical effects, laboratory diagnosis and treatment: literature review" Journal of Xiangya Medicine, 2021; 69(22): 1-14. https://doi.org/10.21037/jxym-21-6

15. Maladkar S, Shankar S, Yadav A, "A Novel Approach for Iron Deficiency Anaemia with Liposomal Iron: Concept to Clinic", Journal of Biosciences and Medicines,2020; 8: 27-41. https://doi.org/10.4236/jbm.2020.89003

16. Rivella S, "Iron metabolism under conditions of ineffective erythropoiesis in b-thalassemia" The American Society of Hematology, 2019; 133(1): 51-58. https://doi.org/10.1182/blood-2018-07-815928 PMid:30401707 PMCid:PMC6318430

19. Benson AE, Shatzel JJ, Ryan KS, Hedges MA, Martens K, Aslan JE, Lo JO. The incidence, complications, and treatment of iron deficiency in pregnancy. Eur J Haematol. 2022 Dec;109(6):633-642. https://doi.org/10.1111/ejh.13870 PMid:36153674 PMCid:PMC9669178

20. Camaschella C. Iron deficiency. Blood. 2019 Jan 3;133(1):30-39. doi: 10.1182/blood-2018-05-815944. Epub 2018 Nov 6. Erratum in: Blood. 2023 Feb 09;141(6):682. https://doi.org/10.1182/blood.2022018610 PMCid:PMC10023716

21. Animasahun BA, Itiola AY, "Iron deficiency and Iron deficiency anaemia in children: physiology, epidemiology, aetiology, clinical effect, laboratory diagnosis and treatment: Literature review" Journal of xiangya medicine, 2021;6(22). https://doi.org/10.21037/jxym-21-6

20. Sandra E Juula, Richard J Dermanb, Michael Auerbach, "Perinatal Iron Deficiency: Implications for Mothers and Infants", Neonatology,2019;115: 269-274. https://doi.org/10.1159/000495978 PMid:30759449

21. Cappellini MD, Musallam KM, Taher AT, "Iron deficiency anaemia revisited", The Association for the Publication of the Journal of Internal Medicine,2020;287, 153-170. https://doi.org/10.1111/joim.13004 PMid:31665543

22. Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, São Paulo, "Iron deficiency anaemia in children: a challenge for public health and for society", Sao Paulo Medicine Jornal, 2005; 123(2): 88-92.

23. Brady PG. Iron deficiency anemia: a call for aggressive diagnostic evaluation. South Med J. 2007 Oct;100(10):966-7. https://doi.org/10.1097/SMJ.0b013e3181520699 PMid:17943034

24. Agarwal AM, Rets A, "Laboratory approach to investigation of anaemia in pregnancy" International journal for laboratory hematology, 2021; 41(1): 65-75. https://doi.org/10.1111/ijlh.13551 PMid:34288450

26. Sundararajan S, Rabe H. Prevention of iron deficiency anemia in infants and toddlers. Pediatr Res. 2021 Jan;89(1):63-73. https://doi.org/10.1038/s41390-020-0907-5 PMid:32330927

27. Gian Carlo Di Renzo, Filippo Spano, Irene Giardina, Eleonora Brillo, Graziano Clerici & Luis Cabero Roura, "Iron deficiency anaemia in pregnancy" Womens Health, 2015;11(6): 891-900. https://doi.org/10.2217/whe.15.35 PMid:26472066

28. Babker AM, Di Elnaim EO, Hematological changes during all trimesters in normal pregnancy, Journal of Drug Delivery and Therapeutics. 2020;10(2):1-4 https://doi.org/10.22270/jddt.v10i2.3958

28. Beladen CC, Botezatu SP, "Anaemia and Management of Heart Failure Patients" Heart failure clinics, 2021; 17(4): 195-206. https://doi.org/10.1016/j.hfc.2020.12.002 PMid:33673945

30. Ning S, Zeller MP. Management of iron deficiency. Hematology Am Soc Hematol Educ Program. 2019 Dec 6;2019(1):315-322. https://doi.org/10.1182/hematology.2019000034 PMid:31808874 PMCid:PMC6913441

31. Lopez A, Cacoub P, Macdougall JC, Peyrin-Biroulet L, "Iron deficiency anaemia" The Lancet, 2016; 387(10021): P907-916. https://doi.org/10.1016/S0140-6736(15)60865-0 PMid:26314490

31. Kumar A, Sharma E, Marley A, Samaan MA, Brookes MJ, "Iron deficiency anaemia: pathophysiology, assessment, practical management" BMJ journals, 2022. https://doi.org/10.1136/bmjgast-2021-000759 PMid:34996762 PMCid:PMC8744124

32. Elstrott B, Khan L, Olson S, Raghunathan V, DeLoughery T, Shatzel J J, "The role of iron repletion in adult iron deficiency anaemia and other diseases" European journal of haematology, 2020; 104(3): 153-161. https://doi.org/10.1111/ejh.13345 PMid:31715055 PMCid:PMC7031048

33. Chaparro CM, Suchdev PS, "Anaemia epidemiology, pathophysiology, and etiology in low- and middle-income countries" Annals of the New York Academy of Sciences, 2019; 1450(1): 15-31. https://doi.org/10.1111/nyas.14092 PMid:31008520 PMCid:PMC6697587

34. Nikolaoua M, Chrysohooub C, Georgilasc TA, Giamouzisd G, Giannakoulase G, Karavidasf A, Papadopoulosg C, Patsilinakosh S, Tziakasi D, Parissis J, "Management of iron deficiency in chronic heart failure: Practical considerations for clinical use and future directions" European Journal of Internal Medicine, 2019; 65: 17-25. https://doi.org/10.1016/j.ejim.2019.05.011 PMid:31109847

35. Benson BS, Shah A, Stanworth SJ, Frise CJ, Spiby H, Lax SJ, Murray J, Klein AA, "The effect of iron deficiency and anaemia on women's health" Association of Anaesthetist, 2021;76(4): 84-95. https://doi.org/10.1111/anae.15405 PMid:33682105

36. James AH, "Iron Deficiency Anaemia in Pregnancy", Clinical Expert Series, 2021; 138(4): 664-674. https://doi.org/10.1097/AOG.0000000000004559

37. Kaushal S, Priya T, Thakur S, Marwaha P, Kaur H, "The Etiology of Anaemia Among Pregnant Women in the Hill State of Himachal Pradesh in North India: A Cross-Sectional Study", Cureus, 2022; 14(1): 1-7. https://doi.org/10.7759/cureus.21444

38. Lanser L, Fuchs D, Kurz K, Weiss G, "Physiology and Inflammation Driven Pathophysiology of Iron Homeostasis-Mechanistic Insights into Anaemia of Inflammation and Its Treatment" Nutrients, 2021; 13(11): 1-29. https://doi.org/10.3390/nu13113732 PMid:34835988 PMCid:PMC8619077

39. Franceschi LD, Iolascon A, Taher A, Cappellini MD, "Clinical management of iron deficiency anaemia in adults: Systemic review on advances in diagnosis and treatment" European Journal of Internal Medicine, 2017;42:16-23. https://doi.org/10.1016/j.ejim.2017.04.018 PMid:28528999

40. Svenson N, Bailey J, Durairaj S, Dempsey-Hibbert N, "A simplified diagnostic pathway for the differential diagnosis of iron deficiency anaemia and anaemia of chronic disease" International Journal of Laboratory Hematology, 2021;43:1644-1652. https://doi.org/10.1111/ijlh.13666 PMid:34288431

41. Cotter J, Baldaia C, Ferreira M, Macedo G, Pedroto I, "Diagnosis and treatment of iron-deficiency anaemia in gastrointestinal bleeding: A systematic review" World Journal Gastroenterology, 2020; 26(45): 7242-7257. https://doi.org/10.3748/wjg.v26.i45.7242 PMid:33362380 PMCid:PMC7723662

42. Garzon S, Cacciato PM, Certelli C, Salvaggio C, Magliarditi M, Rizzo G, "Iron Deficiency Anaemia in Pregnancy: Novel Approaches for an Old Problem" Oman Medical Journal, 2020; 35(5): https://doi.org/10.5001/omj.2020.108 PMid:32953141 PMCid:PMC7477519

43. Gómez-Ramírez S,Brilli E, Tarantino G, Girelli D, Muñoz M, "Sucrosomial® Iron: An Updated Review of Its Clinical Efficacy for the Treatment of Iron Deficiency", Pharmaceuticals, 2023, 16(6), 847; https://doi.org/10.3390/ph16060847 PMid:37375794 PMCid:PMC10305423

44. Auerbach M, "Optimizing diagnosis and treatment of iron deficiency and iron deficiency anaemia in women and girls of reproductive age: Clinical opinion" International Journal of Gynecology and Obstetrics, 2023;162(2):68-77. https://doi.org/10.1002/ijgo.14949 PMid:37538014

45. Rakanita Y, Sinuraya RK, Suradji EW, Suwantika AA, Syamsunarno MRAA, Rizky Abdulah R, "The Challenges in Eradication of Iron Deficiency Anaemia in Developing Countries" Systematic Review Pharmacy, 2020; 11(5): 383-401. http://dx.doi.org/10.5530/srp.2019.2.04

46. Lo JO, Benson AE, Martens KL, Hedges MA, McMurry HS, DeLoughery T, Aslan JE, Shatzel JJ, "The role of oral iron in the treatment of adults with iron deficiency" European journal of haematology, 2023;110:123-130. https://doi.org/10.1111/ejh.13892 PMid:36336470 PMCid:PMC9949769

47. Liberal A, Pinela J, Vívar-Quintana AM, Ferreira ICFR, Lillian Barros L, "Fighting Iron-Deficiency Anaemia: Innovations in Food Fortificants and Biofortification Strategies" Foods, 2020; 9(12):1871. https://doi.org/10.3390/foods9121871 PMid:33333874 PMCid:PMC7765292

48. Camaschella C, "Iron deficiency" Blood, 2019;133(1): 30-39. https://doi.org/10.1182/blood.2022018610 PMCid:PMC10023716

49. Benson AA, Shatzel JJ, Ryan KS, Hedge MA, Martens K, Aslan JE, Lo JO, "The incidence, complications, and treatment of iron deficiency in pregnancy" European journal of haematology, 2022;109 ( ):633-642. https://doi.org/10.1111/ejh.13870 PMid:36153674 PMCid:PMC9669178