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# IRON DEFICIENCY ANEMIA: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY, DIAGNOSIS, AND MANAGEMENT

Pharmaceutical Science

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## ABSTRACT

Iron deficiency anemia (IDA) is the most common nutritional disorder worldwide and a major public health concern, particularly in developing countries. It affects children, women of reproductive age, and pregnant women disproportionately. IDA results from inadequate iron intake, increased requirements, impaired absorption, or chronic blood loss. Iron plays a crucial role in oxygen transport, cellular metabolism, and neurological development. This review summarizes the epidemiology, etiology, pathophysiology, clinical manifestations, and current therapeutic approaches to IDA, including oral and intravenous iron therapies. Recent advances in iron metabolism and the role of hepcidin are also discussed to provide a comprehensive understanding of disease management.

## KEYWORDS

Iron deficiency anemia, hepcidin, ferritin, intravenous iron, ferric carboxymaltose, iron metabolism

## INTRODUCTION

In regular clinical practice, iron deficiency and iron-deficiency anemia are prevalent medical diseases and worldwide health issues. Iron deficiency continues to be the leading cause of anemia globally, despite a recent slight decline in its prevalence. Iron deficiency anemia has a significant impact on the lives of young children and premenopausal women in both developed and low-income nations [1]. Children with hemoglobin levels less than 11 g/dL Anemia is defined as 11.5 g/dL in children aged 6 to 59 months, 12 g/dL in children aged 5 to 11 Lower limits for anemia can be set at 12–14 years of age, for women over 15, and 13 g/dL for men over 15[2]. Malaria, other viral and parasitic disorders, folate and vitamin B12 deficits, and other nutritional inadequacies can all cause anemia in these nations. Pregnant women with severe anemia are less likely to survive obstetric difficulties during and after childbirth, and their kids may be born prematurely or with low birth weights [3]. Reduced formation of red blood cells as a result of inadequate iron levels in the body is known as iron deficiency anemia[4]. Enzymatic reactions, DNA synthesis, oxygen transport, and mitochondrial energy production are just a few of the cellular processes that depend on iron. As a result, IDA symptoms can differ greatly. Reduced blood oxygen levels can cause angina, palpitations, tachycardia, exhaustion, and shortness of breath [5]. Additionally, iron is essential for the central nervous system's growth and development, particularly in children. Brain development, myelination, the activity of monoamine neurotransmitters, and the metabolism of neuronal and glial energy all depend on iron [6]. People with chronic inflammation, malignancy, or renal illness have iron-restricted erythropoiesis and functional ID. This is because, regardless of iron storage, inflammatory activities hinder the delivery of iron to red cell precursors, and the mobilization of iron from stores is insufficient to satisfy metabolic demands. Additionally, this can be seen after receiving erythropoiesis-stimulating medication [7]. Many circumstances, including peripartum blood loss, gastrointestinal bleeding, and uterine or placental bleeding, can exacerbate pregnancy anemia. In addition to the general effects of anemia, there are particular hazards for both the mother and the fetus during pregnancy, including increased risk for peripartum blood transfusion, intrauterine growth retardation, preterm, and feto-placental miss-ratio[8]. There are three types of anemia microcytic, normocytic, and macrocytic, While macrocytic anemia is uncommon in children, microcytic iron deficiency anemia is frequently the cause of anemia in children [9].

## EPIDEMIOLOGY

### GLOBAL EPIDEMIOLOGY OF INDIA

As of March 31, 2017, data on population, health, and nutrition for India, each state and union territory (UT), and 707 districts are available in the National Family Health Survey 2019-21 (NFHS-5), the fifth in the NFHS series. The Ministry of Health and Family Welfare (MoHFW), Government of India, is in charge of conducting all five NFHS surveys [10].

One major public health problem is the incidence of anemia in India. According to the National Family Health Survey 5 (2019–21), the prevalence of anemia among Indian men between the ages of 15 and 49 was 25.0%, but in women in the same age range, it was significantly higher at 57.0%. The frequency among teenage females and boys between the ages of 15 and 19 was 59.1% and 31.1%, respectively. The frequency was 52.2% in pregnant women aged 15–49 years and 67.1% in children aged 6–59 months [11].

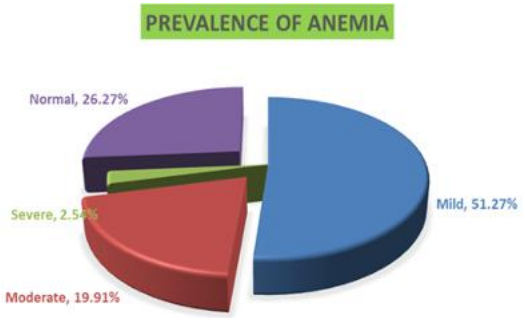


**Figure1. Iron Deficiency Anaemia Prevalence in Adolescent Girls**

## CAUSES

Excessive iron loss, increased iron requirements during growth, and insufficient iron intake and absorption can all lead to iron shortage. Menstruation puts women of reproductive age (WRA) at higher risk, while pregnancy and childbirth generate a net iron loss of 580 to 680 mg due to placental and fetal needs as well as bleeding during delivery [12]. Three primary processes lead to anemia: blood loss, hemolysis (the breakdown of red blood cells), and inadequate erythropoiesis (the body producing insufficient red blood cells). The most frequent causes of anemia are illnesses, nutritional deficits, and hereditary hemoglobin abnormalities [13]. Atrophic gastritis and celiac disease, can also lead to decreased iron absorption [14]. Hepcidin, which sequesters iron and decreases its availability for erythropoiesis, is a common mechanism via which chronic inflammatory diseases, such as heart failure, inflammatory bowel disease, and chronic kidney disease, can hinder iron intake or usage. Neonates and young children who drink cow's milk instead of breast milk are more likely to develop iron-deficiency anemia [15]. Other less common causes like When red blood cells degrade in the bloodstream, iron is released and subsequently excreted in the urine. This condition is known as intravascular hemolysis. People who exercise vigorously, especially jogging, occasionally experience this. Small blood vessels in the feet may be injured as a result, a condition known as "March hematuria." Other illnesses that can cause intravascular hemolysis include heart valve injury and uncommon conditions such diffuse intravascular hemolysis (DIC) or thrombotic thrombocytopenia purpura (TTP) [16]. The risk of anemia can be increased by the existence of additional micronutrient deficiencies, such as those in vitamins A and B12, folate, riboflavin, and copper [13].

## PATHOPHYSIOLOGY

### IRON ABSORPTION AND METABOLISM

Iron is a vital micronutrient needed for cellular respiration, DNA synthesis, and oxygen transport. Because both excess and shortage can result in serious clinical problems, the body closely regulates the balance of iron [17,18]. The duodenum and proximal jejunum are the primary sites of iron absorption, which is impacted by physiological demand and food composition [19]. There are two types of dietary iron, heme iron from animal sources, which is effectively absorbed (15–35%).Plant-based non-heme iron is absorbed less effectively (2–10%) [20]. Divalent metal transporter 1 (DMT1) carries non-heme iron ($Fe^{3}$ ) into enterocytes after duodenal cytochrome B reduces it to $Fe^{2}$ at the intestinal brush barrier [21]. Ferrous iron is released when heme iron is broken down intracellularly after being absorbed via heme carrier protein [19]. Iron is either discharged into circulation by ferroportin or stored as ferritin within enterocytes [22]. After ferroportin-mediated export, hephaestin oxidizes $Fe^{2}$ to $Fe^{3}$ , which enables binding to transferrin in plasma [23]. Transferrin binds to absorbed iron and carries it to tissues such muscles, liver, and bone marrow. Through transferrin receptors, cells absorb transferrin-bound iron, which is then endocytosed and released intracellularly [19]. Ferritin and hemosiderin are the main forms of iron that are stored in the liver, spleen, and bone marrow [20]. Ferritin serves as a readily accessible iron reserve and guards against iron poisoning [18].In the reticuloendothelial system, macrophages recycle the majority of bodily iron from senescent red blood cells. Iron is released during hemoglobin breakdown and is either stored or returned to circulation through ferroportin [24]. Hepcidin, a peptide hormone produced by the liver, is the primary modulator of systemic iron homeostasis .Elevated hepcidin levels reduce iron absorption and release by inhibiting ferroportin. Iron availability is increased by decreased hepcidin [25]. Iron storage, inflammation, erythropoietic activity, and hypoxia all affect hepcidin production .Since iron has no controlled excretion pathway; equilibrium is preserved by controlling intake. Menstruation, skin desquamation, and epithelial shedding all result in daily iron loss [26,27].

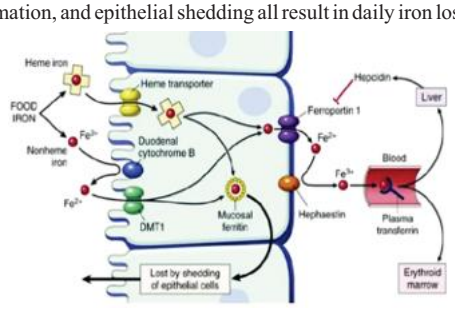


**Figure2. Iron absorption and metabolism in the body.**

## CLINICAL FINDINGS

The World Health Organization defines anemia as a drop in blood hemoglobin to a concentration below 13 g/dL for males and 12 g/dL for women [28]. A number of hematological and biochemical indicators, including TSAT levels, ferritin, and hemoglobin, are evaluated in order to also diagnose IDA. The age, sex, and pregnancy status of each particular marker determine the cutoff [29]. The most reliable sign of iron deficiency is ferritin, and IDA can be diagnosed only by low ferritin. Since ferritin is an acute phase protein, it increases in the presence of infection, cancer, or persistent inflammation. Iron is stored intracellularly as ferritin [30]. For the diagnosis of iron deficiency, bone marrow aspiration is still considered the gold standard. Although it is very specific and unaffected by inflammation, it is invasive, costly, painful for the patient, and affected by recombinant human erythropoietin. As a result, bone marrow aspiration is only used in extremely specific situations where alternative methods are ineffective or problematic. The most sensitive indicator of iron deficiency in individuals with chronic renal disease is hypochromic red blood cells as a percentage of total red blood cells [31].

## MANAGEMENT

### ORAL PREPARATION

In cases of absolute iron shortage, iron salts including iron sulfate, fumarate, and gluconate continue to be a key component of treatment [32]. Adults with iron deficiency anemia must take 120 mg of elemental iron daily for three months; children must take up to 60 mg daily, or 3 mg per kilogram [33]. The elemental iron content determines the dosage (for example, 325 mg ferrous sulphate includes 105 mg elemental iron). Gastrointestinal side effects limit the use of ferrous salts for iron treatment. Ferrous salts exacerbated gastrointestinal symptoms, including constipation (12%), nausea (11%), and diarrhea (8%), according to a systematic evaluation of placebo-controlled trials [34]. Lower dosages can be given to adults using either intermittent dosing (e.g., second daily to weekly) or intermediate-dose tablets (containing around 30–60 mg of elemental iron); the latter strategy has been suggested by the WHO for some developing nations Food [35]. contains phosphates, phytates, and tannates that hinder iron absorption, iron pills should not be taken with food. When taken with iron, ascorbic acid (250–500 mg) may improve absorption by creating an acidic environment [36].Ferrous gluconate and ferrous fumarate. These are also utilized, particularly for those who are intolerant of ferrous sulfate. In general, the dosage is Adults should consume 100–200 mg of elemental iron daily, typically in separate doses. The recommended daily dosage for children is 3–6 mg of elemental iron per kilogram of body weight, depending on their age and weight [37].

### IV PREPARATION

IV iron preparations are made up of an iron core at the center of a carbohydrate shell. The amount of iron that can be injected is limited by the less stable shells of iron sucrose or iron gluconate. Higher iron doses can be administered because ferumoxytol, ferric carboxymaltose, and ferric derisomaltose have more stable shells that release iron gradually [28]. The indications for intravenous iron delivery have historically been restricted by the potential for hypersensitivity reactions (including anaphylaxis) to high-molecular-weight iron dextran [1]. A commonly used IV iron formulation for the treatment of ID, with or without anemia, is ferric carboxymaltose (FCM; Ferinject®, Injectafer®). It is made up of a colloidal solution of nanoparticles with a carboxymaltose-stabilized polynuclear iron (III)-(oxyhydr)oxide core. Ferric derisomaltose (FDI; Monofer®, Monoferric®) is a stable iron (III)–isomaltoside complex intended for IV use that permits administration of doses up to 1000 mg over approximately 20 minutes. This preparation's ability to administer a high dose of iron—up to 750 mg in the US and 1000 mg in the EU—over a brief 15-minute infusion. The super paramagnetic iron oxide nanoparticle ferumoxytol (Feraheme®) was first created as an MRI contrast agent[38].

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