

Iron Deficiency in Children Can Impair Growth and Contribute to Anemia

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Abstract: Iron deficiency Anemia is a kind of anemia that happens when your body doesn't have enough iron. This type of anemia is the most prevalent, and it is currently one of the biggest global public health problems. Globally, it affects both preschoolers and school-age children; it is the primary source of anemia and contributes to physical and neuro-developmental morbidity. Iron deficiency, both with and without anemia, is a common issue in youngsters. In undeveloped countries, children and expecting women are disproportionately affected by iron deficiency anemia, the most severe nutritional deficit in the world. Along with anemia, iron deficiency can result in a myriad of other symptoms. An iron shortage results from inadequate intake, high turnover, or excessive loss. In contrast, inadequate intake is the most common reason for insufficiency, particularly in kids. Blood loss also contributes to iron deficiency and has three leading causes: menstruation, hookworm infection, and cow's milk enteropathy. As a result, the root cause must be effectively controlled during treatment, and more iron must be replenished. Through public awareness efforts and dietary modifications that improve children's availability to iron, the focus has been made on preventing iron deficiency in the western world. This review discusses the diagnostic procedures in both cases with and without anemia, concentrates on the iron deficiency symptoms that are most likely to occur with anemia, and provides treatment recommendations.

Keywords: Iron Deficiency, Anemia, Clinical Features, Iron Supplementation

1. Introduction

All body tissues must have iron for healthy development and operation. Heme proteins that contain iron are involved in energy metabolism and oxygen transport to tissues. Iron and several enzymes which contain iron are used to form myelin, neurotransmission and are also used in the brain for energy metabolism [1]. Anemia is derived from ancient Greek, meaning "lack of blood." Anemia is known as the lack of hemoglobin or the number of red blood cells. Due to anemia, healthy blood cells can't be produced. Inadequate iron intake, persistent blood loss, or a combination of the two are the typical causes of iron deficiency anemia. Iron deficiency is one of the most common cases among other micronutrients [2]. According to the World Health

Organization (WHO), nutritional anemia is a condition in which the blood's hemoglobin content is lower than what is deemed normal for the person's age, gender, physiological state, and altitude, regardless of what caused the shortfall in necessary nutrients [3, 4]. The most prevalent nutritional issue in infancy is this deficiency, which affects populations not just in underdeveloped but also in highly industrialized nations [5, 6]. Women of childbearing age are also afflicted by iron deficiency anemia. One of the problems doctors encounter most frequently is iron insufficiency. While most instances are easy to diagnose and manage, substantial advancements have been achieved in the previous ten years regarding the phenotype of iron deficiency, its diagnosis, and its treatment. Estimating the precise prevalence of iron insufficiency is challenging due to its sluggish onset. As a result, anemia is frequently utilized as a stand-in. According

to estimates from the World Health Organization (WHO), anaemia, which has iron deficiency as its primary cause, affects 47% of children in pre-school and 25% of children in school worldwide, with the highest prevalence occurring between 1 and 3 years of age. No area is exempt; even in the US, 16% of adolescent girls and 9% of children aged 1 to 3 are affected.

2. Global Iron Status and Prevalence of Insufficiency

Iron deficiency has long been considered an effective form of malnutrition worldwide. But lack of consensus exists regarding the nature and severity of the adverse health effects of iron shortage in communities. However, most experts concur that existing public health and nutrition strategies are ineffective at controlling iron deficiency in impoverished populations [7, 8]. Iron deficiency is a malnutritional concern worldwide, but it severely affects children and infants. ID (iron deficiency) poses a life-threatening risk to those. In addition, children who are iron deficient are substantially more likely to experience behavioral issues and developmental impairments [9].

Usually, several biomarkers are considered for judging a person's iron status. Iron, transferrin, transferrin saturation, ferritin, and soluble transferrin receptor are standard biomarkers. Low serum ferritin content is typically related to iron insufficiency diagnosis [10]. One study shows that in Europe, lower socioeconomic status increased the likelihood of ID in babies aged 6–12 months. For instance, 26% of 10-month-old French infants from socioeconomically deprived families were deficient in iron, in contrast to 10% of infants from homes not at risk of socioeconomic disadvantage.

Another point suggests that the type of milk infants also impacted ID prevalence: breast milk or cow milk. Turkish infants aged six months who had human milk or formula had an iron deficiency of 3–4% compared to 25% of newborns who drank cow milk [11].

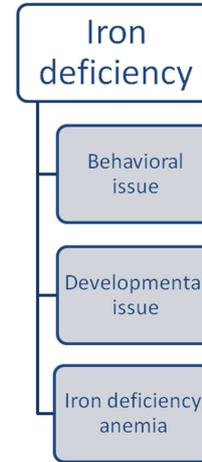


Figure 1. Effects of Iron deficiency.

3. Importance of Iron for Children

Adequate iron demand is essential for the physiological development of children. It is a pre-condition for the overall healthy development of the children. In addition, it is necessary for making a strong immune response [12]. In low- and middle-income nations, young children are regularly exposed to physical difficulties and environmental dangers that could affect their development and health in the future.

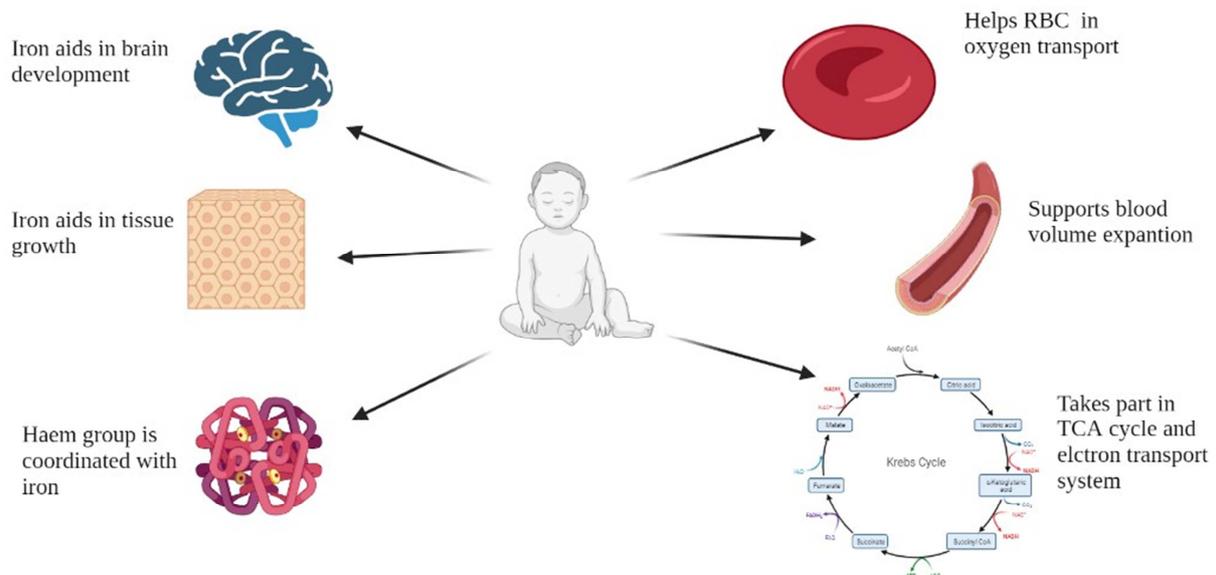


Figure 2. Importance of Iron for Children (This image was created with <https://BioRender.com>).

In this situation, they suffer from various nutritional deficiencies. ID or Iron deficiency is ubiquitous among them.

ID is best known for causing anemia, particularly in LMICs [13]. Except for anemia, ID causes various developmental

and neurological delays in children because of its various essential activities [12].

4. Erythropoiesis in Early Childhood

About 70% of the iron in a good neonate's body is found in hemoglobin, which is more concentrated in infants than adults. Erythropoietic production dramatically reduces after birth due to the shift to a hypoxic environment. In the first two months, hemoglobin levels substantially reduce due to lower erythrocyte lifespan, growth-related diffusion impacts, and other reasons [14]. Iron is reallocated from dormant red cells to iron reserves in combination with this "biological anemia of infancy" [12]. As a result, daily iron demand is typically higher and more important during early childhood.

4.1. The Burden of Anemia in Children

Typically, hemoglobin values below specific criteria are used to define anemia. For children under the age of five, the World Health Organization (WHO) recommends measures of 100-109 g/L, 70-99 g/L, and 70 g/L, respectively, to distinguish mild, moderate, and severe anemia [15]. To prevent anemia in children, iron status is pretty essential.

4.2. Nucleotide Biosynthesis and TCA cycle

DNA replication requires a substrate, provided by nucleotide biosynthesis, dependent on RnR (Ribonucleotide reductase), a di-iron monooxygenase. And in the TCA cycle, iron-sulfur clusters are as central cofactors in energy production. Children's metabolic rate is higher, so they need more iron [12].

4.3. The Function of Iron in Brain Development

Iron, a transition metal that can carry oxygen and shift electrons, is a facilitator in the catalytic site of oxidases, oxygenases, and certain antioxidants. Due to iron's vital role in fundamental physiological functions, including aerobic

phosphorylation and energy consumption, all cells require iron [16]. More and more experts agree that the early years of life, particularly the time between term birth and two years of age, are crucial for brain development. In the first year of life, cortical and subcortical grey matter also experience significant expansion [17].

4.4. The Amount of Iron Children Need

A reserve of iron is present in neonates during birth; this iron comes from the mother during pregnancy while the child is still in the womb. Breastfed babies will acquire all their nutritional value from their mother's milk for the first six months after birth. Use a store-bought iron-fortified baby formula for the first 9 to 12 months if breastfeeding is not an option. After that, it ought to be a cow's milk-based formula. The number of iron babies requires on their age after they begin eating solid meals [18].

Table 1. Amount of iron recommended according to the age (Source: Health Canada, Dietary Reference Intakes (www.hc-sc.gc.ca/fh-an/nutrition/reference/table/ref_elements_tbl_e.html).

Age	Amount of iron per day (recommended daily allowance)
7-12 months	11mg
1-3 years	7mg
4-8 years	10mg
9-13 years	8mg
14-18 years	11mg (for boys) and 15mg (for girls)

5. Consequences of Iron Deficiency in Children

Infants and young children frequently lack iron, particularly in underdeveloped nations. For example the metabolism, neurotransmission, myelination, and gene and protein profiles are all altered by iron insufficiency during the brain's growth surge. Once more, there is substantial evidence to indicate that 6-to 24-month-old babies with iron deficiency anemia are at risk for impaired cognitive, motor, and social-emotional development [19].

Table 2. Iron deficiency consequences on children's development.

Issue	Various cases	Citation
Brain development	Neurodevelopmental dysfunction is associated with ID.	[12]
	Axon myelination is reduced.	[20, 21]
	Reduction in cytochrome c oxidase in a particular brain region	[22, 23]
	Decreased metabolic activity and detrimental impact on memory processing.	[16]
	Establishment of nervous system that is even sensitive to moderate hypoxia.	[23]
Social development	Glabella reflex, Babinski reflex, plantar grasp, an involuntary reflex of arms and legs, and misaligned neurological reflexes are observed in many premature babies with low iron storage (serum ferritin $\leq 76 \mu\text{g/L}$).	[24]
	Less co-operative.	[25]
	Lack of confidence.	
Oxygen carry	Reduced capacity for communication and learning.	[19]
	Negatively affects the transport and retention of oxygen	
Immunity	Failure of body's immune system function.	[16]
	Disrupted innate immune system as iron is vital for innate cells to operate. For example, the effector function of neutrophils is iron-dependent.	[26]
	Iron is vital for certain components of cellular expansion and the disrupted metabolic efficiency of adaptive immunity.	[27]
	The new description of a rare inherited coupled immunodeficiency offers the most solid evidence for iron's pivotal role in adaptive immunity. Furthermore, this defect strikingly hindered T/B cellular proliferation and immunoglobulin class-switching, contributing to the illness.	[28]

Issue	Various cases	Citation
Skeletal and cardiac muscle	Dysfunction	[29, 30]
Physical growth	Poor physical growth	[31]
Overall problems	Blue sclerae, zinc deficiency, gastrointestinal symptoms, pagophagia, anemia, fatigue, poor concentration and memory, greater infection risk or recurrence, tiredness, weakness, dry skin and brittle nails, heart palpitations, headaches and dizziness, restless leg syndrome, red, inflamed tongue (glossitis), abnormal cravings for dirt and shortness of breath.	[32-39]

6. Iron Deficiency Affects Growth

Iron insufficiency is the most prevalent nutritional deficit, affecting 20% to 50% of the world's population [40]. About half of all incidents of anemia in women and children in developing nations are related to iron deficiency [41]. Nearly half of all incidents of anemia in women and children in developing countries are related to iron deficiency. In youngsters, an iron shortage takes time to manifest and causes few serious complications. However, they have slow weight gain, persistent respiratory and gastrointestinal illnesses, and are susceptible to pica. The most concerning is the relationship between iron deficiency and slowed behavior, cognitive, and psychomotor skill development. Last year, a group of specialists concluded that "a large amount of relevant material related to iron deficiency anemia and infant development" [19, 40]. Severe, prolonged iron insufficiency in infancy is routinely linked to youngsters who perform worse cognitively and score worse on academic achievement tests, demonstrating that a deficit at a pivotal time of brain development and differentiation leads to irreparable problems [42]. Infants with acute, sustained iron deficiency did worse on tests of their mental and physical skills, according to a study done on 11–14-year-old Costa Rican children who had been examined and treated for an iron deficiency. They indicated a lag or distortion in the change in cognitive processing typical of childhood and adolescence [42, 43].

7. Anemia Due to Iron Deficiency

Iron deficiency is the most prevalent dietary shortfall in children, impacting more than 25% of the world's population [44, 45]. It primarily affects youngsters between 0 and 5 and young mothers who are pregnant. Lack of iron can have fatal consequences for red blood cell synthesis, muscular function, and energy expenditure [46]. Iron deficiency is insufficient iron in the body to support regular physiological activities [47]. A lack of iron causes anemia without enough iron; the body is unable to make enough hemoglobin, a crucial component of red blood cells, which transports oxygen in our body. Lack of iron results in hemoglobin shortage in the body; because of these factors, bone marrow also struggles to create enough hemoglobin [48]. However, Iron deficiency anemia may or may not be present with iron deficiency and still impact the tissue [47, 49]. Inadequate ingestion leads to iron insufficiency, either high turnover or loss. Since insufficient intake is the most frequent cause of iron deficiency in children [50], with rapid development, low birth weight, and

gastrointestinal upsets from consuming too much cow's milk and cow's milk protein also Encouraged colitis [47, 49]. It is also important to take into account malabsorption disorders such as celiac disease and inflammatory bowel disease that cause decreased absorption of iron. According to a study up to 46% of Celiac patients have decreased bodily iron storage, and 32% have an iron deficiency. Celiac disease causes iron deficiency because "gluten" damage the upper intestine, which is also essential for absorbing iron [51, 50]. Another typical contributor to childhood anemia is inflammation. Regardless of the precise source of inflammation, most kids with moderately severe acute inflammation see a significant decline in Hgb within a week of the disease's start [52]. Iron deficiency is further brought on by excess blood loss in childhood [50], for example, Meckel's diverticulum where bleeding occurs and leads to iron deficiency anemia. Some drugs also lead to anemia in children such as Acetylsalicylic acid, Glucocorticoids, NSAIDs [53, 54]. Infection can also cause anemia such as *Ancylostoma duodenale* (Hookworm infection), this parasite, which affects red blood cells (RBCs) in many ways, causes anemia, especially in children and nematodes infection in the intestine, malaria infection, certain autoimmune diseases also cause anemia [50, 54, 55]. Some genetic factors such as Iron-refractory iron-deficiency anemia also underlying conditions in iron deficiency anemia [54, 56]. Iron deficiency and iron deficiency anemia is a significant global public health issue that mostly affects newborns, young children, and women of reproductive age in underdeveloped nations and childrens are most vulnerable to iron deficiency anemia. Some factors that create children to most prone to develop iron deficiency anemia are: rapid growth, prenatal risk factors, inadequate iron rich food intake, and gastrointestinal bleeding brought on by an excessive intake of cow's milk, hookworm infection, Febrile Seizure [45, 54, 57].

Rapid growth: This anemia develops because the baby's body is overgrowing, and it takes time for red blood cell production to catch up. As a result, red blood cells are destroyed by the body too fast. This issue frequently arises when the mother's and the infant's blood types differ [45].

Perinatal risk factors: Various conditions can lower a baby's iron reserves at birth or operate via other mechanisms, increasing the likelihood of the baby having IDA in the first few months of life. These conditions are prematurity, maternal anemia, maternal hypertension with intrauterine growth restriction or diabetes during pregnancy, use of erythropoietin for preterm anemia, fetal-maternal bleeding, twin-twin transfusion syndrome, various perinatal hemorrhagic episodes, and inadequate dietary iron intake during the first few months

of life are among these diseases [45, 47].

Dietary factors: In early infancy and childhood, feeding and related nutritional considerations are crucial since they can significantly influence IDA development. A variety of dietary variables can affect the metabolism of iron. The most frequent causes include inadequate iron intake, impaired iron absorption, ingesting unprocessed cow's milk before one year, and occult intestinal blood loss brought on by colitis caused by cow's milk protein [47]. Infant formula or transitional meals without an iron fortification are typically the cause of newborns' inadequate iron consumption throughout infancy. In the Chilean research, babies fed iron-free formula had a greater incidence of IDA (about 20%), newborns provided iron-fortified formula had a significantly lower prevalence (around 0.6%), and infants fed human milk had a median majority (about 15%) [58]. Children who consume a vegetarian diet frequently struggle with IDA [45].

Gastrointestinal disease: Most of the dietary iron is absorbed in the duodenum. Conditions that affect this area of the gut, such as celiac disease, Crohn's disease, giardiasis, and resection of the proximal small intestine, resulting in

gastrointestinal malabsorption of iron. Further testing with tissue transglutaminase antibodies has been highly advised since anemia caused by iron, folic acid, and vitamin B12 malabsorption in children is a typical consequence of celiac disease [47].

Febrile Seizure: In children, anemia and febrile seizures are both prevalent conditions. Compared to kids with a febrile illness without seizures, kids with febrile seizures are approximately twice as likely to have iron deficiency anemia [57].

Hookworm infection: Children are particularly vulnerable to hookworm infection because they frequently play in the soil with bare hands and wander around barefoot. This parasite, which affects red blood cells (RBCs) in many ways, causes anemia, particularly in youngsters. For example, hookworms eat RBCs and generate intestinal bleeding, which is suitable for developing new blood cells and anemia [59, 60]. Reduced production, increased breakdown (hemolysis), or loss (hemorrhage) are the primary issues impacting RBCs that lead to anemia when homeostatic processes malfunction. [61]

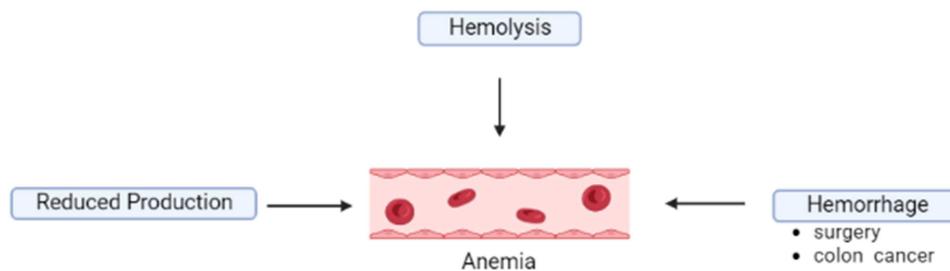


Figure 3. Mechanism of Anemia (This image was created with <https://BioRender.com>).

Table 3. Factors related to children's anemia.

Factors	Cause	Example	Reference
Internal	Physiologic		
	Increased demand	Infancy, Quick development.	[49, 54]
Internal and external	Environmental	Poor or inadequate iron reached diet, poverty, malnutrition, consuming too much cow's milk, low birth weight.	[48, 49, 54]
	Pathologic		
Internal	Decreased absorption	Celiac disease, inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease), helicobacter pylori infection, duodenal/gastric ulcers.	[45, 50, 51, 54]
	Chronic blood loss	Esophagitis, Gastritis, peptic ulcer, benign tumors, intestinal cancer, hookworm infection, hemorrhoids.	[54]
External	Drug-related	Glucocorticoids, NSAIDs (nonsteroidal anti-inflammatory drugs), aspirin, and Antibiotic such as Cephalosporin.	[45, 53, 54]
Internal	Genetic	Iron-refractory iron-deficiency anemia	[54, 56]
Internal	Congenital causes	Diamond-Blackfan anemia, Aase syndrome, Pearson marrow pancreas syndrome	[62]
Internal	Acquired causes	Transient erythroblastopenia of childhood	[62]

8. Immunological Function of Iron

The immune system and iron are closely related and are crucial for immune surveillance because of their ability to induce immune cell proliferation and differentiation and their interference with cytokines and cell-mediated immune effector pathways [63, 64]. The relation between iron and the immune system can be described in many aspects: firstly, many of the genes and proteins involved in iron homeostasis

are crucial in regulating iron fluxes, which prevents bacteria from using iron for growth; secondly, cells of the innate immune system, monocytes, macrophages, microglia, and lymphocytes, can defend against bacterial assaults by carefully regulating their iron fluxes, which are controlled by ferroportin and hepcidin. Thirdly, several effector molecules, including toll-like receptors, NF-B, hypoxia factor-1, and haem oxygenase, will coordinate the inflammatory response by releasing a wide range of cytokines, neurotrophic factors, chemokines, and reactive oxygen and nitrogen species [64].

According to experimental findings from the last decades, iron is a vital component for the healthy development of the immune system. Lack of it impairs the ability to maintain a sufficient immunological response and reduces immunoprotective pathways. Iron is essential for immunity because it promotes the growth of immune cells, particularly lymphocytes, which are linked to the production of a particular immunological response to infection. Iron deficiency seems to have less of an impact on cellular immunity than on humoral immunity [65, 66]. Iron is necessary for the differentiation of monocytes into macrophages, and macrophages need iron as a cofactor to carry out crucial antimicrobial effector processes, such as the nicotinamide adenine dinucleotide phosphate hydrogen-dependent oxidative burst [67]. Iron deficiency anemia leads to reduced T-cell proliferation. Because iron is necessary for enzymes like ribonucleotide reductase and DNA synthesis, it is required for the proliferative phase of lymphocyte activation, which can be decreased during IDA [68, 69]. Significant impacts of ID on cellular immunological activities, including reduced levels of CD3, CD4, and CD4/CD8 ratio, have been found in recent research on pregnant women [70]. Iron deficiency and iron deficiency anemia also increase the susceptibility to infection; over 40%

of children with iron deficiency anemia worldwide commonly develop infections because ID has been linked to impaired immunity, which raises vulnerability to infectious disorders [71, 72]. Iron deficient children may experience abnormal leukocyte and lymphocyte functions as well as abnormal interleukin (IL)-2 and IL-6 production [73, 74]. Inversely, having too much iron might make us more susceptible to specific bacterial infections. Iron builds up in immune cells, which hinders their ability to fight against bacteria, and some bacteria thrive in environments with a lot of iron. In addition, the bacteriostatic properties of the iron-binding proteins transferrin and lactoferrin are lost when the proteins become iron-saturated [75]. The quantities of iron that cells are exposed to should be controlled appropriately since iron insufficiency and excess can impair cellular function. Different effects of iron supplementation on susceptibility to infection and immunity can be seen in communities with high rates of iron deficiency and IDA. Malaria is connected to anemia, and changes in iron metabolism during a malaria infection may affect susceptibility to co-infections, although low iron status may protect against malaria infection [76]. A recent study showed that taking supplemental iron did not raise the chance of malaria. [77]

Table 4. Conditions of iron deficiency with treatment strategies.

Condition	Intervention	Doses	Population	Reference
Iron Deficiency in Children	Dietary Supplement: Iron Syrup Other: Placebo	<12µg/L ferritin on iron syrup	Child	[78]
Colon Cancer, Chronic Constipation	Dietary Supplement: BioFe		Adult	[79]
Restless Legs Syndrome	Dietary Supplement: BioFe		Adult	[80]
Cancer	Drug: Ferinject	20ml/week		[81]
Iron Deficiency	Diagnostic Test: Non-invasive measurement of ZincProtoporphyrin IX			[82]
Malnutrition	Other: BioFe Medical Food			[83]
Iron Deficiency	Dietary Supplement: Ferrous gluconate		Infant	[84]
Iron Deficiency Anemia	Diagnostic Test: Baseline Ferritin Level Drug: Ferrous Sulfate Drug: Lactoferrin	Ferrous Sulfate: 300-600 mg/day (initial) or, 120mg/day (elemental) Lactoferrin: 100mg/day	Pregnant	[85]
Iron Deficiency	Drug: Quadruple sequential Helicobacter pylori eradication + iron sulfate Drug: Quadruple sequential Helicobacter pylori therapy Drug: Ferrous Sulfate Drug: Placebo	Ferrous Sulfate: 15-30 mg/day (initial) or, 3-6 mg/day (elemental)	Children	[86]
Superoxide dismutase and glutathione peroxidase in erythrocytes	Drug: Vitamin E			[87]

Since 1960, there has been a marked decrease in the prevalence of nutritional iron deficiency anemia in newborns and toddlers [88].

8.1. Preterm Infants

About 0.5 mg/L of iron can be found in human milk [89]. For the first four to six months of life, human milk provides all the iron that full-term infants need, but for preterm infants' erythropoiesis and growth, more iron is required [90]. Therefore, iron supplementation is neither advised nor

needed during the adjustment period right after birth [91].

8.2. Breastfed Infants

Until 4 to 6 months, infants born on time typically had enough iron in their bodies [92]. Iron deficiency can be avoided by giving breastfed infants supplemental iron (ferrous sulfate) at 7 mg daily between 1 and 5.5 months of age [93].

8.3. Toddlers

Late infancy (7–12 months); 11 mg/day; recommended

dietary requirement for total iron consumption (mg/d) [94]. Dietary iron is a common supplement given to expectant mothers and the main component of infant formulae. Liver, legumes, beans, nuts, green leafy vegetables, and fortified cereals are foods high in iron content. However, their bioavailability varies greatly [95].

9. Measures of Iron Status

Serum-based indicators such as erythrocyte protoporphyrin, serum ferritin, transferrin saturation, and soluble transferrin receptor are used in the biochemical assessment of iron status (STFR) [96].

Table 5. Iron status indicators.

Indicators	Iron Deficiency Anemia (IDA)	Anemia of Chronic Disease (ACD)	Both IDA & ACD Condition	Overload	Reference
Erythrocyte Protoporphyrin	↑	↑	↑	↓	[97]
Serum Ferritin	↓	↑	Normal	↑	[98]
Transferrin Saturation	↓	↓	↓	↑	[99]
Soluble Transferrin Receptor	↑	Normal	↑	Normal	[100]
Hepcidin	↓	↑		↓	[101]

Note: ↓ = Reduced, ↑ = Increased

10. Conclusion

Because of their fast development and blood volume increase at a time when their meal may contain only a trace of iron, infants are one of the most vulnerable to iron deficiency anemia. Although iron deficiency anemia remains a major problem in certain American babies, the prevalence of iron deficiency anemia has decreased considerably in the United States over the last 20 years. The iron shortage is relatively common due to insufficient iron intake, particularly in developing countries. In affluent nations, the prevalence of these illnesses is lower than in emerging countries. Children's brain development can be significantly impacted by early-life iron insufficiency, which is frequent. Thus, measures to lower the risk of early iron insufficiency and brain dysfunction are crucial for public health. The first line of treatment for iron insufficiency in children must be oral iron supplements. However, parenteral iron supplementation is used when oral iron therapy is ineffective for treating iron deficiency anemia in patients or when a quick replacement of iron levels and iron storage is required. In children, parenteral iron is well tolerated. Iron supplements can be a good option for the children who is suffering from the iron deficiency due to its cost efficacy. But this supplementents can cause some health issues for the children.

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