Outline of Iron Deficiency Anemia among Pediatrics

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Abstract

Background: Iron deficiency (ID) is a status in which iron amount in the body is less than the amount required to maintain normal physiologic functions. It is a result of inadequate iron absorption or a consequence of prolonged negative iron balance, both can lead to decreased iron stores as measured by serum ferritin (SF) concentrations or iron content in bone marrow. The main characters of IDA are the symptoms of lethargy, dizziness, and weakness and the signs of pallor in the skin or mucous membranes. Nothing of these manifestations is specific or sensitive. Because ID tends to develop slowly, adaptation occurs and the disease frequently goes undetected for some time. However, in severe cases, dyspnea can occur. Diagnosis of ID is difficult, and the combination of several iron status indicators seems to provide the best assessment of iron sufficiency. Low levels of serum iron, serum ferritin and transferrin saturation are a direct combination for diagnosis of ID. However, the same diagnosis can become a challenge if other inflammatory diseases are present. While oral iron is safe, affordable, and easy to administer, patients often suffer from intolerable gastrointestinal side effects. The WHO recommends that children with iron deficiency anemia be given 6 mg/kg/d elemental iron (ferrous fumarate or sulfate), orally as a single dose or divided into 2 or 3 doses, for 2 months. Therapy with iron supplements has some gastrointestinal side effects, such as abdominal discomfort, nausea, vomiting, constipation, and dark colored stools. Enteric-coated and delayed-release iron supplements are made to increase compliance, as they cause less side effects; however, they are not as well absorbed as the non-enteric-coated preparations.

Keywords: Iron deficiency anemia, Pediatrics

Introduction

According to **WHO (1),** Anemia is a condition in which the number of red blood cells or the hemoglobin concentration within them is lower than normal. Hemoglobin is needed to carry oxygen and if there is few or abnormal red blood cells, or not enough hemoglobin, there will be a decreased capacity of the blood to carry oxygen to the body's tissues. This results in symptoms such as fatigue, weakness, dizziness and shortness of breath.

Iron deficiency (ID) is a status in which iron amount in the body is less than the amount required to maintain normal physiologic functions. It is a result of inadequate iron absorption or a consequence of prolonged negative iron balance, both can lead to decreased iron stores as measured by serum ferritin (SF) concentrations or iron content in bone marrow **(2)**.

Iron deficiency anemia (IDA) is a more severe state in which iron levels are low with presence of hypochromic microcytic anemia. Therefore, it is important to consider treatment before anemia develops **(3)**.

Iron deficiency (ID) and iron-deficiency anemia (IDA) are common health problems that affects children under the age of five. Although the prevalence of IDA has recently decreased to some extent, ID remains the top-ranking cause of anemia worldwide, and IDA has a considerable effect on the lives of young children in both developing and developed countries **(4).**

Stages of Development of Iron Deficiency and Iron Deficiency Anemia:

Sequential changes in the amount of iron present in the various iron compartments of the body result in development of ID **(5).**

- ✓ **In the First Stage***:* Iron stores become depleted but the body still has enough iron to meet the needs of red cell production.
- ✓ **In the Second Stage:** Iron stores are depleted and the amount of iron in the circulation starts to decrease and red cell production becomes affected (iron deficient erythropoiesis).
- ✓ **In the Third and Final Stage*:*** Iron stores are depleted, the amount of iron in circulation is very low and red cell production is markedly reduced with development of anemia**.**

Incidence and Prevalence of Iron Deficiency and Iron Deficiency Anemia:

The incidence of ID and IDA is high in infancy. It is assessed that almost half of children aged less than 5 years in developing countries are suffering from iron deficiency (40-50%). Iron-deficiency anemia is most prevalent in low socioeconomic groups- although no socioeconomic group is out of danger- and IDA is less prevalent in Caucasian children than in African-American children. Multiple studies were done in Egypt to recognize the extent of ID and IDA. IDA is the most common cause of anemia among Egyptian infants 6 to 24 months old of low socioeconomic standard. The prevalence of anemia among preschool children (<5years) ranged from 39.6% to 52.2% **(6)**.

Children from rural areas, those from low social class and those of low maternal educational level had a higher risk for IDA than other children. Infants with IDA were found to consume foods with low content of iron approximately 50% below recommended daily needs. Sixty four percent (64%) of children visiting outpatient clinics were found to have IDA **(7).**

Causes of ID and IDA:

During intrauterine period, the only source of fetus to get iron is through the placenta. In the end of pregnancy, the total iron in the fetus is 75 mg/kg. Physiological anemia occurs in the postnatal period and if there is no significant blood loss, iron stores will be enough to provide erythropoiesis in the first six months of life. Delayed clamping of the umbilical cord may enhance the iron state and decreases the ID risk later on (**1)**

The amount of iron in the breast milk is at the maximum level in the first month and it keeps declining progressively in the following periods to reach about 0.3 mg/L at the fifth month **(8).**

- ✓ **Physiological Factors That Increase The Risk of ID and IDA:**

1) ***Increased iron needs***: Low birth weight (LBW), prematurity and multiple gestations.
2) ***Blood loss:*** From perinatal bleeding like in cases of placenta Previa.
3) ***Dietary factors:*** Early cow's milk intake, early solid food intake, low-iron formula, frequent tea intake, low intake of vitamin C, low intake of meat, breast feeding more than six months without iron supplements and low socioeconomic status with frequent infection. Infants at higher risk are those older than 6 months with exclusive breast-feeding and infants from 9 to 18 months of age if fed with cow's milk or low-iron-content formulas. After 18 months of age, the risk of ID is reduced due to regular diet and the reduced growth rates, so lower iron requirements **(5).**

Pathological Causes That Increase The Risk of ID and IDA:

1) ***Blood loss:*** From digestive tract, surgery, hematuria, epistaxis and hemoptysis or from hemodialysis.
2) ***Malabsorption:*** Celiac disease, gastrectomy, H. pylori, gut resection, atrophic gastritis, pica syndrome, interaction with food like tea, coffee, calcium or oxalates and phytates.
3) ***Chronic diseases:*** Chronic heart disease, cancer, chronic renal failure, rheumatoid arthritis, obesity and inflammatory bowel disease.

4) ***Genetic disorders:*** Iron refractory iron deficiency anemia, divalent metal transporter deficiency anemia, fanconi anemia and pyruvate kinase deficiency.

The commonest causes of IDA observed in children are insufficient intake together with rapid growth, low birth weight and gastrointestinal losses due to extreme cow's milk intake **(1).**

Cow's milk (CM) may lead to ID due to low iron content of CM, which makes it difficult for infants to get their iron requirements needed for growth, occult intestinal blood loss accompanied with CM consumption during infancy and decreased absorption of non-heme iron by calcium and casein present in high amounts in CM. Several cases of iron deficiency anemia (IDA) have been reported in infants and toddlers that were considered to result from excessive cow's milk consumption **(9).**

The prematurity of infancy prompts negative iron balance by several factors. Iron accumulation occurs mainly during the last trimester of gestation. Total body iron, total hemoglobin contents, serum iron concentrations and stored iron concentrations are lower in preterm infants. Severe maternal ID, intrauterine growth restriction, and chronic blood loss during pregnancy can additionally compromise the amount of fetal iron. Postnatal, the scanty iron stores can be rapidly depleted during the first 6-8 weeks, due to the onset of erythropoiesis and the rapid catch-up growth. Hemoglobin nadir occurs earlier in premature infants **(10).**

Infection with intestinal helminthes either cause blood loss or interfere with absorption of iron in the intestine. Infection with soil-transmitted helminths, especially roundworms (Ascaris lumbricoides), hookworms (Necator americanus and Ancylostoma duodenale), and whipworms (Trichuris trichiura) increases incidence of iron deficiency anemia **(11).**

H. pylori have been proposed as a cause for cases of unexplained IDA refractory to iron therapy. It is thought that iron consumption by the bacteria, blood loss from gastrointestinal tract and decreased iron absorption by gastric acidity may be the reason behind IDA in cases with H. pylori infection. The eradication of H. pylori infection prior to IDA treatment in cases with positive H. pylori serology is important as well **(12).**

Iron deficiency anemia affects approximately 45% of patients with inflammatory bowel disease (IBD), negatively impacts the quality of life in this patient population, and significantly burdens their systems. The pathogenesis of iron deficiency in IBD patients is multifactorial, including intestinal bleeding, malabsorption, and inadequate oral intake **(13).**

Iron deficiency (ID) with or without anemia is a very common complication of inflammatory bowel disease (IBD), with a prevalence of more than 70% in the children. Anemia in IBD is a combination of ID and anemia of inflammation (AI) i.e. anemia of chronic disease (ACD), which is triggered by negative effects of an activated immune system at different stages of erythropoiesis. Besides ID and ACD, metabolic disturbances and vitamin deficiencies as well as commonly used IBD drugs can increase the risk of anemia in IBD **(14).**

Anemia is a common comorbidity in patients with chronic kidney disease (CKD). The prevalence of anemia increases with increasing severity of kidney dysfunction. In people with CKD stages 3, 4 and 5 approximately 20%, 60% and 70% respectively, are anemic.The primary cause of anemia in CKD is erythropoietin deficiency, but iron deficiency can aggravate the grade of anemia and reduce the response to erythropoietin-stimulating agents (ESAs) **(15).**

Clinical Manifestations of Iron Deficiency Anemia:

The main characters of IDA are the symptoms of lethargy, dizziness, and weakness and the signs of pallor in the skin or mucous membranes. Nothing of these manifestations is specific or sensitive. Because ID tends to develop slowly, adaptation occurs and the disease frequently goes undetected for some time. However, in severe cases, dyspnea can occur **(5)**.

Other symptoms and signs of iron-deficiency anemia include :

- ✓ **Gastrointestinal Tract (GIT) Symptoms:** Anorexia, pica, atrophic glossitis, dysphagia, esophageal webs and reduced gastric acidity.

Central Nervous System (CNS) Symptoms: Irritability, fatigue, lower mental and motor developmental test scores, decreased attentiveness, lower school performance and decreased cognitive performance.
Cardiovascular System (CVS) Symptoms: Angina and palpitation.
Musculoskeletal System Symptoms: Impaired performance of a brief intense exercise task, decreased physical performance in prolonged endurance work and adverse effect on fracture healing.
Diagnostic Investigation:
Diagnosis of ID is difficult, and the combination of several iron status indicators seems to provide the best assessment of iron sufficiency. Low levels of serum iron, serum ferritin and transferrin saturation are a direct combination for diagnosis of ID. However, the same diagnosis can become a challenge if other inflammatory diseases are present **(16).**

Biochemical Markers for IDA:

Hemoglobin*:* Hemoglobin is below the acceptable level for age.
Table (1): Age-Based Mean hemoglobin Levels in Children **(17)**

Age	**Mean Hemoglobin (g/L)**	**-2 Standard Deviation**
Birth (term infant)	165	135
1 month	139	107
2 months	112	94
3- 6 months	115	95
6 months- 2 years	120	105
2-6 years	125	115
6-12 years	135	115
Males	145	130
Females	140	120

Table (2): Mean hemoglobin concentrations for the diagnosis of anemia and assessment of severity **(1)**

Age	**Anemia (g/L)**		
	Mild	Moderate	Severe
6- 59 months	100-109	70-99	Lower than 70
5- 11 years	110-114	80-109	Lower than 80

12- 14 years	110-119	80-109	Lower than 80

Red Cell Indices:

These include decreased mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) for age. Mean corpuscular volume (MCV) is the mean volume or the average size of all the RBCs in the sample. It is calculated by dividing the hematocrit (volume of all RBCs) by RBCs number **(18).**

The value is expressed in femtolitres ($fL=10^{-15}$ L). The normal range is 80-94 fL. Mean corpuscular hemoglobin (MCH) represents the average mass of Hb in one RBC and is expressed in picograms ($pg=10^{-12}$ gr). It is calculated by dividing the total mass of Hb by the number of RBCs. The normal range is 27–31 pg. Mean corpuscular hemoglobin concentration (MCHC) is the mean concentration of Hb in the RBCs or the average concentration of Hb in one liter of RBCs. It is calculated by dividing the Hb by the hematocrit. The normal range is 31.5–35 g/dl **(18).**

Generally, the decrease in the red cell indices parallels the decrease in hemoglobin. In long-lasting anemia, red cells are microcytic and hypochromic, as shown by low MCV and MCH. Hypochromic microcytic anemia is caused by any factor that decreases the body's iron stores. Hemoglobin is a globular protein that has four globin chains attached to porphyrin ring (heme) the center of which contains ferrous iron. Reduced iron stores stop the production of hemoglobin chains, and its concentration begins to decrease in the newly formed RBCs. Hemoglobin is the cause of the red color of RBCs, so its reduction causes the color of the new RBCs to fade thus the name, hypochromic. The decrease in the amount of hemoglobin in the new RBCs causes their size to be smaller when compared to normal RBCs, thus the name, microcytic**.** Red cell distribution width (RDW) is a parameter that measures variation in red blood size or red blood cell volume (anisocytosis). Any disease involving RBCs destruction or production increases the variability in RBCs size and leads to RDW elevation. Systemic inflammatory response resulting from different etiologies can alter both erythropoiesis and erythrocyte maturation thus causing an acute rise in RDW **(19).**

✓ **Reticulocyte Hemoglobin Content (CHr):**

Erythrocytes have a long lifespan of 120 days so they are late indicators of ID. However, reticulocytes only remain in blood for 1–2 days so CHr is considered a good marker of functional ID **(20).** CHr evaluates the iron amount available for erythropoiesis in the preceding 3-4 days **(**3**).**

Serum Ferritin:

Serum ferritin is one of the commonest used and definite biomarkers of iron status in young children; reflecting body iron stores. Serum ferritin is an acute-phase reactant, and concentrations of serum ferritin may increase in cases of chronic inflammation, infection, malignancy, or liver diseases. A serum ferritin level <30 ng/mL is the most sensitive (92%) and specific (98%) cutoff level for the diagnosis of absolute ID, with or without anemia**.** Ferritin concentration below 30 ng/mL in children and 70 ng/mL in adults may be used to indicate iron deficiency **(1).**

Serum Iron, Total Iron-Binding Capacity and Transferrin Saturation:

Serum iron concentration can be measured directly and usually declines after depletion of iron stores. However, serum iron may not express iron stores accurately due to the effect of other several factors such as infection and inflammation. Activation of immunity in such cases diverts iron from the erythropoietic bone marrow to the storage sites, particularly the liver and spleen causing iron-limited erythropoiesis and anemia **(5).**

Total iron-binding capacity (TIBC) estimates the availability of iron binding sites. Extracellular iron is transferred in the body bound to transferrin. Hence, TIBC indirectly measures transferrin levels, which increase as serum iron concentration decreases. Also, TIBC is diminished with malnutrition, inflammation, chronic infection and cancer **(5).**

Transferrin saturation (TSAT) shows the proportion of occupied iron binding sites and reflects iron transport rather than storage. TSAT is calculated through dividing serum iron concentration by TIBC, expressed as a percent **(21).**

Table (3): Hematologic markers for identifying Iron deficiency **(22)**

Biochemical Marker	**Normal**	**ID without Anemia**	**ID with Anemia**
Serum Ferritin (g/L)	Normal (100 ± 60)	Decreased (<10)	Decreased (<10)
Serum Iron (g/L)	Normal (115 ± 50)	Decreased (<60)	Decreased (<40)
Total Iron Binding Capacity (mcg/dL)	Normal (330 ± 30)	Normal or Increased (390-410)	Increased (>410)
Transferrin Saturation (%)	Normal (35 ± 15)	Decreased (<20)	Decreased (<10)

Prevention of ID and Iron Deficiency Anemia :

The American Academy of Pediatrics (AAP), the WHO and other well-known pediatrics organizations introduced many recommendations for prevention of ID and IDA. These recommendations include screening infants in the 9-12th months in terms of ID, enrichment of foods with iron, supplementing iron-rich formulas when breast milk is unsatisfactory, avoiding cow's milk in the first year of life, and giving infants iron prophylaxis **(23).**

It is suggested that the low quantity of iron in human milk is satisfactory for the exclusive breastfeeding early in life. The WHO recommends exclusive breastfeeding for the first 6 months, and the AAP recommends exclusive breastfeeding for at least 4 months but preferably for 6 months. Exclusive breastfeeding for more than 6 months has been related to higher risk of IDA at 9 months of age **(1).**

Supplementation leads to improved visual acuity and advanced Bayley Psychomotor Developmental Indices at 13 months. Thus, for term infants who are exclusively breastfed, it is recommended to receive an iron supplementation of 1 mg/kg per day, beginning at age of 4 months and continued till suitable complementary foods containing iron have been introduced **(24).**

WHO recommended daily iron supplementation with 2 mg/kg daily of elemental iron made for children aged between 1-5 years and 30- 60 mg daily for children aged between 5-12 years to prevent ID **(1).**

Treatment of Iron Deficiency Anemia:

✓ **Oral Iron Therapy:**

While oral iron is safe, affordable, and easy to administer, patients often suffer from intolerable gastrointestinal side effects **(13).**

The WHO recommends that children with iron deficiency anemia be given 6 mg/kg/d elemental iron (ferrous fumarate or sulfate), orally as a single dose or divided into 2 or 3 doses, for 2 months **(25).**

Oral iron supplements are a cost-effective strategy for reestablishing iron balance in iron-deficient patients. Previous studies suggested that combination of iron with vitamin C could benefit iron absorption **(26).**

Dietary vitamin C is strongly recommended to improve non-heme iron absorption from the gut. Also, vitamin C can adjust both cellular uptake and metabolism of iron. In patients with iron overload, vitamin C cycling across the plasma membrane is responsible for ascorbate-stimulated Fe uptake from iron–citrate complexes, which are prominent in the plasma of such patients. Also, vitamin C modulates iron metabolism by increasing the synthesis of ferritin, hindering lysosomal degradation of ferritin, and lessening the efflux of cellular iron **(27).**

There are two classes of iron supplements; those containing the ferrous form of iron and those containing the ferric form of iron. The commonest used iron supplements are those that contain the ferrous form as it is the better absorbed form of the two. The three commonly well-recognized types of ferrous iron supplements are ferrous fumarate, ferrous sulfate, and ferrous gluconate. They vary in the amount of elemental iron (the form of iron in the supplement that is accessible for absorption by the body), and contain 33%, 20%, and 12% iron, respectively. Therapy with iron supplements has some gastrointestinal side effects, such as abdominal discomfort, nausea, vomiting, constipation, and dark colored stools. Enteric-coated and delayed-release iron supplements are made to increase compliance, as they cause less side effects; however, they are not as well absorbed as the non-enteric-coated preparations **(28).**

Iron-containing salts should not be taken with food, because the phosphates, phytates and tanates present in food bind to the iron and affect absorption. Antacids, H2 receptor antagonists, proton pump inhibitors, antibiotics (e.g; quinolones, tetracyclines), and food and drinks containing calcium can also affect the absorption of iron salts. A liquid iron preparation is a better choice for patients suffering from the constipating effect of oral iron therapy. Laxatives, stool softeners, and adequate intake of liquids can lessen this constipation **(28).**

✓ **Intravenous (IV) Iron Therapy:**

Intravenous (IV) iron produces the fastest and the most sustained erythropoietin response. It is indicated when there is intolerance to or non-compliance with oral iron, malabsorption due to surgery, concomitant use of erythropoietin, and anemia secondary to cancer or chemotherapy. Iron sucrose is one of the most commonly used intravenous preparations and associated with very low adverse drug reaction **(29).**

Another IV iron compound is ferric carboxymaltose (FCM). Ferric carboxymaltose is a macromolecular ferric hydroxide carbohydrate complex, which allows the delivery of iron within the cells of the reticulo-endothelial system, and consequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of releasing large amounts of ionic iron in the serum. **(30).**

It is distributed to the bone marrow, liver and spleen and is rapidly cleared from the circulation. It is a stable complex with the benefit of being non dextran-containing and having low risk of anaphylaxis due it very low immunogenic potential. Its properties allow the administration of large doses in a single session (15-minute infusion) without the requirement of a test dose **(30).**

Follow up :

After treating the cause of IDA and returning of hemoglobin concentrations to normal, a full blood count and indicators of iron status should be measured repeatedly. The British Society of Gastroenterology recommends measurements every month for 3 months, and then every 3 months for a year. If symptoms persist, additional blood tests should be done every three months for another year, and iron supplements should be given. If hemoglobin or red cell indices are not maintained in this way, further investigations are mandatory **(31).**

Causes of Iron Therapy Failure : (5)

1) ***Poor compliance.***
2) ***Insufficient iron therapy dose .***
3) ***Inappropriate iron preparation .***
4) ***Inadequate duration.***
5) ***Persistent or unrecognized blood loss*** .
6) ***Improper diagnosis:*** Thalassemia or sideroblastic anemia .
7) ***Concurrent disease that affects iron absorption or utilization:*** (e.g., chronic inflammation, inflammatory bowel disease, malignant disease, hepatic or renal disease, concomitant deficiencies (vitamin B12, folic acid, thyroid)) .
8) ***Impaired gastro-intestinal absorption:*** due to high gastric pH (e.g., antacids, histamine-2 blockers, proton pump inhibitors), Helicobacter pylori and Gluten sensitivity .

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