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Iron Deficiency Anemia (IDA): A Review

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Abstract: ***"Anemia" is described as a group of conditions that result from an inability of erythropoietin tissues to maintain normal hemoglobin concentration on an account of inadequate supply of one or more nutrients leading to a reduction in the total circulating hemoglobin. It can occur due to poor vegetarian diet, malabsorption of iron, hookworm infections, excessive blood loss, menstruation and childbirth. The adverse effects of anemia include low birth weight, reduced immune-competence, poor cognitive development, behavioral complications, reduced work capacity, and maternal mortality. Serum ferritin is the most sensitive and preferred initial diagnostic test for IDA. Dietary diversification, supplementation, and fortification of staple foods and nutrition education, are the best tool to combat iron deficiency anemia.***

Keywords: Anemia, iron deficiency, micronutrient deficiency, nutritional anemia

1. Introduction

Today, Iron Deficiency Anemia (IDA) is the most common micronutrient deficiency in the world, bringing serious economic consequences and obstacles to national development. In India, National Family Health Survey-3 presents the statistics which show that the prevalence of anemia in children is as high as 79 per cent, while 56% of adolescent girls are anemic [1]. Iron deficiency accounts for anemia in 5% of American women and 2% of American men [2]. Iron is essential to virtually all living organisms and is integral to multiple metabolic functions. The most important function is to transport oxygen in hemoglobin [3]. Hemoglobin is an iron-rich protein present in red cells, contains iron that carries the oxygen from the lungs to the rest of the body. Erythropoietin is a glycoprotein hormone synthesized in the kidneys that regulates red blood cell formation. The term "Anemia" (from the ancient Greek ἀναιμία, *anaimia*, meaning 'lack of blood') is used for a group of conditions that result from an inability of erythropoietin tissues to maintain a normal hemoglobin concentration on an account of inadequate supply of one or more nutrients leading to a reduction in the total circulating haemoglobin. For the formation of and normal growth of red blood cells, iron and vitamins, like folic acid, vitamin C, vitamin E, and B_{12} are essential. Anemia can be further classified by RBC size (micro, normo, and macrocytic anemia); RBC shape (Sickle cell anemia) and by etiology (nutritional anemia).

2. Magnitude of the problem

According to World Health Organization [4], globally, anemia affects 1.62 billion people, which corresponds to 24.8% of the population. The highest prevalence is in preschool-age children (47.4%) and the lowest prevalence is in men (12.7%). However, the population group with the greatest number of individuals affected is non-pregnant women (468.4 million). In developing countries every second pregnant woman and about 40% of preschool children are estimated to be anemic.

3. Progression of Iron Deficiency to IDA

3.1 Storage and Transport of Iron

According to the National Health and Nutrition Examination Survey-3 [5] data, iron deficiency is defined by two or more abnormal measurements (serum ferritin, transferrin saturation and/or erythrocyte protoporphyrin). Iron is initially stored as a protein-iron complex called ferritin. Transferrin is a specific globular protein that circulates throughout the plasma pool and transport iron to cells via the transferrin receptor pathway. Transferrin carries iron to the bone marrow where it is accepted into RBCs via a transferrin receptor (CD71) and incorporated into heme for use in hemoglobin. It is important that iron be bound to transferrin because unbound iron is toxic. The concentration of transferrin increases during iron deficiency.

3.2 Stages of IDA

Iron deficiency generally occurs in three sequential stages:-

a) *First Stage - Iron Depletion:* The body has the ability to increase intestinal iron absorption dependent on the body iron needs. This stage is characterized by reduced serum ferritin, reduced iron concentration in the marrow and liver tissue, when there is an insufficient supply of iron due to more iron being lost than is absorbed; but, at this stage, erythropoiesis remains normal as does hemoglobin, serum iron, total iron binding capacity and transferrin saturation. This stage generally has no symptoms, although, patients develop iron deficiency.

b) *Second Stage - Latent Iron Deficiency without anemia*: Substantially reduced iron stores in the bone marrow begin to affect hemoglobin production and iron-deficient erythropoiesis begins. Hemoglobin production declines to the point where anemia develops. However, hemoglobin levels are still normal. At this stage, in addition to already reduced iron stores (decreased serum ferritin), serum iron and transferrin saturation decreases with increased total iron binding capacity (TIBC) and increased free erythrocyte protoporphyrin. Transferrin saturation of less than 15% is a sign of latent iron deficiency, since more iron is now being

released from the circulating transferrin in order to maintain erythropoiesis.

c) *Final Stage - IDA*: This stage begins when the small, hemoglobin-deficient cells enter the circulation in increasing numbers, replacing normal erythrocytes that have grown old and have been removed from the circulation. By this time, the development of iron deficiency anemia is associated with the decreased serum iron, increased TIBC, decreased transferrin saturation and diminished hemoglobin production with the development of progressive microcytic, hypochromic anemia. Hemoglobin concentration falls below the normal threshold for age and sex.

4. Clinical Features

Anemia goes undetected in many people, and symptoms can be small and vague. The signs and symptoms can be related to the anemia itself, or the underlying cause. Most commonly, people with anemia report non-specific symptoms such as; general malaise or weakness, poor appetite, headache, dizziness, lethargy and shortness of breath. On examination, the signs exhibited may include smooth tongue, pallor, pale conjunctivae and koilonychias. Other symptoms are constipation, sleepiness, tinnitus, hair loss, depression, twitching muscles, tingling, numbness, or burning sensations, glossitis, angular chelitis, missed or heavy menstrual cycle. Pica, the consumption of non-food based items such as dirt, paper, wax, grass, ice, and hair, may be a symptom of iron deficiency, although it occurs often in those who have normal levels of hemoglobin [6].

5. Etiology

The causes of anemia in the developing world are multi-factorial. The possible factors leading to iron deficiency are:-

5.1 Inadequate Iron Intake

The term 'nutritional anemia' occurs due to a deficiency in one or several nutrients, mainly iron, folic acid, vitamin B_{12}, protein, and possibly pyridoxine, vitamin C, copper and vitamin E. Anemia due to a deficiency of folic acid (Megaloblastic anemia) is more common than that of vitamin B_{12} deficiency (pernicious anemia) especially during pregnancy, when the demands of the fetus are added to those of the mother.

Apart from pregnancy, deficiencies of folic acid and B_{12} are rare except in malabsorption and in certain diseases of the bowel such as tropical sprue. In public health terms, iron deficiency is by far the first cause of nutritional anemia worldwide [7]. IDA can occur due to inadequate iron intake, secondary to a poor diet such as vegetarian lifestyle with insufficient heme iron (as only 3–5% of dietary iron is absorbed in normal healthy individual).

5.2 Impaired Absorption

Dietary iron is available in two chemical forms: heme iron, which is found in meat; and non-heme iron, which is found in plant and dairy foods. The absorption of heme iron is minimally affected by the composition of meals and gastrointestinal secretions. The absorption of non-heme iron from a vegetarian diet (1-5%) is poor as compared to heme iron (8-10%). Therefore, vegetarian girls, especially after menarche are at higher risk of developing anemia [8].

The bioavailability of non-heme iron requires acid digestion and varies by an order of magnitude depending on the concentration of enhancers (e.g., ascorbate, meat) and inhibitors (e.g., phytates, phosphates, tannins calcium, fiber, tea, coffee and wine) found in the diet. Intake of iron absorption inhibitors results in depleted iron stores. Malabsorption of iron can also occur due to gastrointestinal tract abnormalities and parasitic infections like Helicobacter pylori infection. IDA is also common in elderly, as iron absorption decreases with advancing age.

5.3 Increased Requirements

Deficiency of iron in the diet during periods of accelerated demand like in infancy (rapidly expanding blood volume), adolescence (rapid growth and onset of menstruation in girls) and pregnancy and lactation can result in anemia. The developing brain undergoes rapid structural and functional changes during the perinatal period and requires a regular supply of iron. Failure to meet the iron demands at this critical period or presence of iron excess appears to have long standing and often permanent adverse effects on neurodevelopment. Adolescents of both the sexes are particularly vulnerable to developing anemia because of rapid growth, weight gain, and blood volume expansion and in girls additionally because of onset of menstruation. In girls, middle adolescence growth happens earlier (i.e., during 12-15y) than in boys (i.e., during 13-16y) [9]. As the requirements of iron during pregnancy and losses in menstrual blood are high, the iron requirements of a woman of childbearing age are at least twice than those of a man and post-menopausal woman. In communities where iron deficiency is common, maternal IDA and poor body stores can lead to a low haemoglobin concentration in the cord blood, poor fetal stores of iron and even anemia in early infancy that leads to anemia during adolescence.

5.4 Blood Loss

Blood loss can occur from the gastrointestinal tract or other chronic diseases such as tuberculosis, ulcers or intestinal disorders, heavy, long or frequent menstruation, child birth, frequent blood donations, accidents, hemorrhage, surgery, certain medications and intravascular hemolysis (a condition in which red blood cells break down in the blood stream, releasing iron that is then lost in the urine. This sometimes occurs in people who engage in vigorous exercise, particularly jogging).

5.5 Hookworm Infection and Malaria

Iron-deficiency anemia also results from chronic intestinal blood loss due to hookworm infection often causing long-term morbidity [10]. Much of the burden of hookworm is due to extra-corporeal iron loss, and interventions to treat hookworm infection have demonstrated significant improvements in hemoglobin [11]. Malaria is a major contributor to anemia in the developing world. Though the

primary cause of anemia in the context of malaria is hemolytic, studies have demonstrated that the anemia of inflammation plays an important role as well by inducing changes in iron absorption and distribution [12]. In addition to the excess destruction of erythrocytes by the malarial parasites, repeated malarial infection is also responsible for a chronic anemia associated with an enlarged spleen.

6. Consequences

Chronic anemia may result in behavioral disturbances in children as a direct result of impaired neurological development in infants, and ultimately reduced scholastic performance and poor concentration in children leading to slow social development [6]. A major threat to safe motherhood, it contributes to low birth weight, repeated infections, reduced immune-competence, poor cognitive development, behavioral complications and decreased work capacity. While anemia has well known adverse effects on physical and cognitive performance of individuals, the true toll of iron deficiency anemia lies in the ill-effects on maternal and fetal health, including increased risk of sepsis, maternal and perinatal mortality. Deficits in reading, writing and arithmetic, spatial memory and attention appear to be particularly associated with iron deficiency in infancy. Poor nutritional status and anemia in pregnancy have consequences that extend over generations. Thus, in these adolescent girls, the mother-to-be, who will usher the next generation, pregnancy, only serves to aggravate their pre-existing anemia. One of the commonest causes of maternal deaths (20 per cent) in India during pregnancy is severe anemia [13]. A Substantial proportion of maternal deaths due to ante partum and post-partum hemorrhage, pregnancy induced hypertension and sepsis occur in women with moderate anemia.

Several chronic diseases are frequently associated with iron deficiency anemia—notably chronic kidney disease, chronic heart failure, cancer, and inflammatory bowel disease. In all these diseases this anemia or chronic disease is at least partially due to excessive production of cytokines and leukotrines that interfere both with the effect of erythropoietin (EPO) at the bone marrow and the release of stored iron in the reticulo-endothelial system [14].

7. Diagnosis

Although, the history and physical examination can lead to recognition of the condition and help establish etiology, IDA is primarily a laboratory diagnosis that could be done through four tests: – Serum iron (SI), Serum transferrin saturation (TS) or total iron binding capacity (TIBC), Serum ferritin (SF) and Hemoglobin level (Hb). Among these tests, Serum ferritin is the most sensitive and preferred initial diagnostic test. Total iron binding capacity (TIBC) is often measured at the same time as serum iron. This measurement indicates the potential capacity of transferrin molecules to bind with serum iron. Individuals with risk factors for diabetes, cardiovascular diseases, stroke, liver diseases and cancer face amplified risks proportional to the amount of stored body iron over and above the optimal range. A diagnostic criterion for IDA is given below [21][22][23].

Table 1: Diagnostic criteria for IDA

Tests	*Normal Range*	*IDA*
TIBC	240-450 µg/dL (men & women)	High
SI	55–160 µg/dL (men) 40–155 µg/dL (women)	Low
TS	20%-50% (Adults) >16% (Children)	<12 - 16%
SF	15–200 ng/ml (women) 20–300 ng/ml (men) 25 – 75 ng/ml (Optimal for men and women)	<15ng/ml) (in a healthy person) or <50ng/ml (in a person with an underlying source of chronic inflammation
Hb	130 g/L (men) 120 g/L (women) 110 g/L (pregnant women and preschool children)	Low

8. Prevention and Management

Nutrition intervention strategies that include a long-term focus on balanced nutrition, i.e. dietary diversification, short-term supplementation, medium-term fortification of staple foods with bioavailable iron and nutrition education, are the best tool to combat iron deficiency anemia.

8.1 Dietary Diversification

Dietary modification approaches are designed to increase micronutrient intake. Kitchen gardens should be promoted to increase the availability of, and access to, iron-rich foods. Food habits should be improved to maximize the absorption of iron. Non-vegetarian foods such as meat and organs from cattle, fowl, fish, and poultry; and non-animal foods such as legumes and green leafy vegetables, vitamins A and C rich foods, and folic acid should be included in the diet which enhances the absorption or utilization of iron. Iron absorption inhibitors like tea/coffee should not be consumed along with meals as these can actually reduce the amount of iron that is absorbed. Raw wheat bran can also interfere with the absorption of iron, so this should be avoided too. Every individual has different iron requirements at different age group and conditions; as given in the table below [24]:-

Table 2: Recommended dietary allowances for Indians (ICMR)

Age/Age Group (years)	Iron (mg/day)
Man	28
Pregnant Woman	38
Lactating Woman	30
Non Pregnant Woman	30
Children	
1-3 y	12
4-6 y	18
7-9 y	26
13-15 y	
Boys	41
Girls	28
16-18 y	
Boys	50
Girls	30

8.2 Dietary Supplementation

Though supplementation with iron, folic acid remains a cornerstone in the treatment and prevention of anemia, the addition of vitamin C has its other added advantages. Ascorbic acid reverses the effect of dietary inhibitors and is one of the most powerful known promoters of non-heme iron absorption, which forms the bulk of the Indian's diet.

Amla (Indian gooseberry) and lemon are the richest and cheapest sources of vitamin C. Amla is among the highest known land source of vitamin C, 100 gm of Amla contains about 700 mg of vitamin C, which is thirty times the amount found in oranges. It is 12 times more assimiable and creates more potent medicinal effect than synthetic vitamin C [15][16]. Researchers have also shown that just 8.7 mg of natural vitamin C from Amla is equivalent to 100 mg of synthetic vitamin C [17]. Moreover, Amla is an exception among fruits not only because of its high vitamin C content, but also because it contains substances which partially protect the vitamin from destruction on heating or drying [18].

8.3 Food Fortification

As defined by the WHO [19], fortification refers to "the practice of deliberately increasing the content of an essential micronutrient, i.e. vitamins and minerals (including trace elements) in a food irrespective of whether the nutrients were originally in the food before processing or not, so as to improve the nutritional quality of the food supply and to provide a public health benefit with minimal risk to health. Food fortification of commonly consumed foods, has been identified by the World Health Organization, the Copenhagen Consensus and the Food and Agriculture Organization, has been considered as one of the of the top four strategies for decreasing micronutrient malnutrition at the global level.

An effective iron fortification programme requires the cooperative efforts of governments, the food industry (producers, processors, and marketers) and consumers. Several iron fortificant have been used successfully in a variety of national programmes. When flour is used as a vehicle, the general population is the target group, but this approach does not reach infants and young children, who usually consume little bread. Therefore, novel approaches are clearly needed to provide bioavailable iron in a form that is acceptable to the target population, inexpensive, largely self-sustaining, and economically viable [20].

8.4 Nutrition Education

Emphasis should also be made on imparting nutrition education to improve the diet through increased intake of fruits and vegetables rich in vitamin C. Mothers should be educated to feed breast milk exclusively for the first six months of an infant's life. Emphasis should be made to provide home-based weaning and complementary iron-rich foods to pre-school children.

Cooking practices that increase iron content of the food should be followed, such as fermentation, germination of some foods and cooking in iron utensils. For example, improving food preservation and home or community processing technologies can be especially useful in improving iron status. These interventions are enhanced by efforts to generate additional income for women and by effective nutrition education.

8.5 Iron Therapy

The goals of treating IDA are to treat its underlying cause and restore normal levels of red blood cells, haemoglobin, and iron. Iron supplementation is the most common strategy currently used to control iron deficiency in developing countries. Combined with other micronutrients, folic acid should always be given with iron during pregnancy. Parenteral iron can be used when oral preparations are not tolerated.

Other indirect measures to prevent IDA might include:-

- Prevention of infectious diseases (e.g. diarrhoeal and respiratory diseases, measles).
- Parasitic disease control programmes (hookworms, trichuriasis, aschistosomiasis infestations, and malaria).

Ideally, parasite control should be complemented by primary preventive measures to break the transmission cycle and environmental health measures to reduce parasitism (especially hookworms).This is particularly important for pregnant women, who should receive an appropriate anti-helminthic after the third month of pregnancy.

According to National Nutritional Anemia Prophylaxis Programme (NNAPP) (INDIA), the recommended daily dosages of iron and folic acid (IFA) are given in tablet form as follows [21]:-

Table 3: Supplementation dosages recommended by NNAPP

Age group	Dosage schedule	Duration
Children 6-60 months	2o mg elemental iron + 100 µg folic acid (one tablet of pediatric IFA or 5 ml of IFA syrup or 1 ml of IFA drops)	100 days if the child is clinically found to be anemic.
School children 6-10 years	30 mg elemental iron + 250 µg folic acid	100 days.
Adolescents 11-18 years	100 mg elemental iron + 500 µg folic acid	100 days
Pregnant women	One tablet of 100 mg elemental iron + 500 µg folic acid prophylactically If clinically anemic	Daily 2 such tablets to be given daily for 100 days
Nursing mothers	One tablet OF 100 mg elemental iron + 500 µg folic acid	100 days

9. Conclusion

The policies and programmes for combating micronutrient malnutrition must be firmly rooted in the food based rather than drug based approaches. Special efforts should be made to identify and treat iron deficiency during pregnancy and

early childhood because of the effects of severe iron deficiency upon learning capability, growth, and development. Dietary modifications should be done to improve overall dietary intakes and consumption of iron, folic acid and vitamin C rich foods as well as food items that promote iron absorption. Therefore, nutrition education along with iron supplementation with natural sources of vitamin C is the best strategy to restore normal levels of hemoglobin and iron, thus preventing iron deficiency anemia in the vulnerable population.

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