Understanding the Determinants of Anemia amongst Indian Adolescents

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ABSTRACT

Anemia is the most common nutritional disorder amongst Indian adolescents in India with 28% being afflicted. Despite the efforts, there has not been a significant reduction in the prevalence of anemia. The etiology of anemia is multifactorial and complex. Hence, there is a challenge to address the determinants of anemia in a population. In the present communication, the determinants of anemia such as nutritional factors, infectious diseases, genetic factors and other underlying factors has been reviewed. The pathophysiology, possible mechanisms and contribution of these factors in the etiology of anemia has been discussed. There is a need for analyzing the determinants of anemia amongst Indian adolescents for effective prevention and control of Anemia.

Key words: Anemia, Iron deficiency, Hemoglobin, India, Adolescent

1. INTRODUCTION

Anemia is a major public health problem amongst adolescents in India\(^1\). Adolescents are at a high risk of iron deficiency and anemia due to accelerated increase in requirements for iron due to rapid pubertal growth with sharp increase in lean body mass, blood volume and red cell mass, which increases iron needs for myoglobin in muscles and haemoglobin in the blood. Adolescents, particularly girls, are vulnerable to iron deficiency anemia as there is a regular loss of 12.5-15 mg iron per month or 0.4-0.5 mg iron per day in menstrual blood\(^2,3\).

The requirement for iron increases two to three folds from a preadolescent level (0.7-0.9 mg iron per day) to adolescent (Boys: 1.4-1.9 mg iron per day, Girls: 1.4-3.3 mg iron per day)\(^2,4\). Studies indicate that the incidence of anemia in adolescents tends to increase with age and corresponds with the highest acceleration of growth during adolescence. The highest prevalence is between the ages of 12-15 years when requirements of iron are at peak\(^2,4\). DLHS-2 in India reported that the extent of mild and moderate anemia among adolescent girls diminished gradually with the age from 10-14 to 15-19, but the incidence of severe anemia increased with age\(^5\). According to the CNNS, prevalence of anemia was significantly increased among older adolescents\(^1\). Additionally, female adolescents 12 years of age and older have higher prevalence of anemia as compared to their male counterparts\(^1\).

1.1 Functional consequences amongst adolescents

The functional consequences are known to occur prior to the onset of clinical stage of iron deficiency anemia (IDA)\(^6,7\). The consequences are known to occur even at mild levels of anemia or prior to onset of clinical stage of anemia\(^8\). Anemia has
serious adverse effects on growth and development during school age. IDA was independently associated with decreased cognition, learning ability and lower school achievements amongst adolescent girls.\textsuperscript{9–14} IDA causes marked impairment in oxidative energy production in skeletal muscle.\textsuperscript{2–4} This leads to less efficient glucose oxidation and decreased capacity for physical exercise and work performance.\textsuperscript{15} IDA in adolescence may also impair the immune response, thus making them more prone to infections. A study conducted amongst Indian children aged 1-14 years indicated that the immune response was significantly depressed in those with haemoglobin concentrations below 10g/dl.\textsuperscript{16}

Worldwide, US$50 billion in GDP is lost annually due to physical and cognitive losses related to IDA. In India, where anemia is very prevalent, the lifetime costs of IDA between the ages of 6 and 59 months amounted to 8.3 million disability-adjusted life-years (DALYs) and annual production losses of US$ 24 billion in 2013 (corresponding to 1.3% of GDP).\textsuperscript{17} High prevalence of anemia amongst the large adolescent population of India would have further impact on the GDP as they are on the verge of becoming its immediate workforce.\textsuperscript{18}

1.2 Magnitude of anemia amongst Indian adolescents

National level surveys (DLHS-2 and NNMB) conducted in 2002 documented that the overall prevalence of anemia was in the range of 69-98% amongst adolescent girls using indirect cyanmethemoglobin method.\textsuperscript{5,19} A community based study conducted in 16 districts across India in 2006, estimated the prevalence of anemia in adolescent girls to be 90.1%.\textsuperscript{20} NFHS-3 conducted in the year 2005-2006, reported prevalence of anemia as 56% amongst adolescent girls.\textsuperscript{21} NFHS-4 (2015-2016) reported an insignificant decline (2%) over a decade in the prevalence of anemia amongst adolescent girls in the age group of 15-19 years (54%).\textsuperscript{22} Severe, moderate and mild anemia was prevalent in 1.0%, 11.8% and 41.1% adolescent girls; respectively. Slow decline in anemia was reported in the recently published NFHS-5 report for 22 states/UTs of India.\textsuperscript{23} Community and hospital based studies conducted in India have reported a very high prevalence estimate of anemia (70-90%) (Table 1).

The CNNS (2016-2018) reported that 28% of adolescents aged 10-19 years had some degree of anemia (Figure 1). According to the severity of anemia, 17% had mild anemia, 10% had moderate anemia and 1% had severe anemia. Anemia was significantly higher in adolescent girls (~40%) as compared to boys (~18%). Adolescent girls and boys living in rural areas (29.0%) has higher prevalence of anemia as compared to their urban counterparts (26.8%).

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International Journal of Health Sciences and Research (www.ijhsr.org) Vol.11; Issue: 4; April 2021
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**Table 1: Continued**

**International Journal of Health Sciences and Research (www.ijhsr.org) Vol.11; Issue: 4; April 2021**

Aakriti Gupta et al. Understanding the determinants of anemia amongst Indian adolescents.
Table 1 - Continued

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*Hemoglobin has been estimated using cyanmethemoglobin method (gold standard)

2. Etiology of anemia amongst Indian adolescents

2.1 Nutritional Factors

Nutritional anemia results from insufficient bioavailability of hemopoietic micronutrients and macronutrients needed to meet the demands of hemoglobin and
erythrocyte synthesis. Metabolically micro and macronutrients have an active role in regulation of biosynthetic mechanisms as well as in gene expression particularly in phosphorylation, methylation or epigenetic changes either by xenobiotic or environmentally active compounds.

Inadequate dietary intake of nutrients or dietary inhibitors present in the diet leading to lower absorption and utilization of metabolic nutrients and other nutrient losses (through menstruation, infections) contribute to nutritional anemia. The complex nutritional disturbances, such as those observed in starvation and protein/calorie deficiency states, can also result in nutritional anemia. Vitamin deficiencies that have been reported as causative factors in the development of anemia include vitamin A, vitamin B (folic (B9), cyanocobalamin (B12), pyridoxine (B6), thiamine (B1) and riboflavin (B2)), vitamin C, vitamin D and vitamin E (Table 2). Furthermore, minerals such as iron, zinc, selenium and copper are indispensable for optimal erythropoiesis (Table 2). Although each micronutrient inadequacy has specific roles multiple deficiencies tend to cluster within individuals, and the synergistic effect of these deficiencies is important in the development and progression of anemia and even leads to iron deficiency itself (Table 2).

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<td>Iron</td>
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<td>Zinc</td>
<td>• Impaired erythropoiesis</td>
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<td></td>
<td>• Decreased red cell resistance to oxidative stress, impairing host defense</td>
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<td>Copper</td>
<td>Interference with red cell maturation and iron absorption</td>
<td>73</td>
</tr>
<tr>
<td>Selenium</td>
<td>Oxidative stress or increased inflammation leading to increased hemolysis</td>
<td></td>
</tr>
<tr>
<td>Vitamins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follic Acid</td>
<td>Impaired DNA synthesis, leading to reduced erythropoiesis</td>
<td>76</td>
</tr>
<tr>
<td>Vitamin B9 (Cobalamin)</td>
<td>• Impaired DNA synthesis, cell division and thus erythropoiesis</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>• Interference with folic acid metabolism</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 (Riboflavin)</td>
<td>• Impaired iron mobilization (involved in iron absorption in gut mucosa)</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>• Impaired globin production, leading to impaired erythropoiesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Reduced intestinal absorptive capacity</td>
<td></td>
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<tr>
<td></td>
<td>• Increased iron losses</td>
<td></td>
</tr>
<tr>
<td>Vitamin B6 (Pteroyl)</td>
<td>Impaired haem synthesis, leading to impaired erythropoiesi</td>
<td>77</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>• Impaired haem synthesis, leading to impaired erythropoiesi</td>
<td>77,78</td>
</tr>
<tr>
<td></td>
<td>• Impaired mobilization of iron stores (involved in regulating the availability of iron from liver and spleen stores)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Impaired susceptibility of infection</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Oxidative stress of the erythrocytes leading to increased hemolysis</td>
<td>79</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>• Availability in gut enhances conversion Fe3+ to Fe2+, increasing iron absorption and bioavailability</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>• Reduced mobilization of iron from stores</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Oxidant damage to erythrocytes, leading to hemolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Capillary hemorrhaging, leading to blood loss</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>• Decreased local calcitriol production in the bone marrow, which may limit erythropoiesi</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>• Increased hepcidin levels</td>
<td></td>
</tr>
</tbody>
</table>

**2.1.1. Iron**

Iron is an essential component of hemoglobin in red blood cells and of myoglobin in muscles. The ferric form (Fe3+) of iron is metabolically active and binds to the protein protoporphyrin IX complex to form haem. Inactive and insufficient form of iron thereby results in low body store of iron, low haem production and hemoglobin concentration. This condition represents itself as hypochromic microcytic anemia. Physiologically, iron deficiency occurs when requirements exceed the dietary intake or bioavailability of iron absorbed from the diet. Requirements are...
increased during periods of rapid increase in body mass (such as in pregnant women, young children) or by high losses of iron (menstruation, hookworm infection). Impaired iron absorption and utilization as a result of repeated infection and/or concomitant micronutrient deficiencies also leads to iron deficiency. This explains the high prevalence of anemia in vulnerable groups such as children and pregnant women, and on the other hand, the association of anemia with poverty and poor health. 

Iron absorption is low (~5%) from plant-based diets (developing countries) due to the presence of non-heme iron and active inhibitors such as phytates, polyphenols, oxalates, and tannins. Millets (ragi, sorghum), beans, some vegetables, and condiments contribute tannins which are strong inhibitors of iron absorption. Oxalates in vegetables, carbonates, phosphates and dietary fiber also interfere with iron absorption. The absorption of iron from habitual mixed cereal-pulse habitual diet is 5% (men and children) and 8% (all women). However, iron in animal products is bound in heme protein structures that greatly facilitate the absorption to approximately 15% from animal based diets (developed countries).

The latest NNMB 2012 report suggested that more than 60% of the Indian adolescent boys and girls consumed less than 50% RDA of iron. Only 20% of them consumed more than 70% of the RDA for iron. The low iron intake is further worsened by the low bioavailability of non heme iron present in primarily cereal-based Indian diets. The prevalence of anemia has been reported to be higher in Indian adolescents consuming a vegetarian diet (45.8%) as compared to those consuming a mixed diet, which includes animal food (30%).

The recent CNNS survey reported that 21.5% of the adolescents in the age group of 10-19 years has low ferritin levels. The prevalence of iron deficiency declined with increasing age amongst male adolescents but increased steadily with age amongst females due to menstruation. Girls had almost a three times higher prevalence of iron deficiency as compared to adolescent boys (31% vs. 12%). Around 12% of adolescents had anemia and iron deficiency, 10% were iron deficient but not anemic, and 17% had anemia but no iron deficiency.

A systematic review suggested that mild to moderate iron deficiency, even without established anemia, has adverse functional consequences. The intergenerational transfer of poor iron status from mother to child has also been shown in several studies. Iron deficiency amongst adolescent girls being future mothers increases the vulnerability of infants to iron deficiency and anemia as they are born with reduced or deficient pools of iron stores. This reflects on the interplay between both the perinatal and other etiologic factors in the causation of anemia.

The latest WHO report and other systematic reviews contradict the earlier notion of iron deficiency being the highest contributor of anemia. Only approximately 50% of cases of anemia are considered to be due to iron deficiency, but the proportion probably varies among population groups and in different areas, according to the local conditions. A recent meta-analysis of data from 23 low and middle income countries found that iron deficiency accounts for only 25 percent of anemia in young children and 37 percent of anemia in women of reproductive age. They documented that the proportion of anemia associated with iron deficiency was lower in countries where anemia prevalence was >40%, especially in rural populations (14% for pre-school children; 16% for non-pregnant women of reproductive age), and in countries with very high inflammation exposure (20% for pre-school children; 25% for non-pregnant women of reproductive age).

A systematic review documented that change in Hb with iron supplementation was 0.74 g/dL. Projections suggested that,
on average, between 37.9% and 62.3% of baseline anemia (Hb <11 g/dL) was responsive to iron supplementation among children under 6 years of age; the corresponding range for malarial hyperendemic regions was 5.8% to 31.8%.

A meta-analyses suggest that iron supplementation could increase the mean blood hemoglobin concentration by 8.0 g/L (95% Confidence Interval (CI): 5.0-11.0) in children, 10.2 g/L (95% CI: 6.1-14.2) in pregnant women and 8.6 g/L (95% CI: 3.9-13.4) in non-pregnant women. Applying these shifts to estimated blood hemoglobin concentrations, indicates that about 42% of anemia in children and about 50% of anemia in women would be amenable to iron supplementation. Hence, other etiological factors need to be investigated.

2.1.2 Folic acid and Vitamin B₁₂

Nutrient deficiency of either folate or vitamin B₁₂ leads to decreased synthesis of deoxy-ribonucleoprotein (DNA) during red blood cell production. This results in a condition in which the bone marrow produces formation of large, structurally abnormal, immature red blood cells with poorly differentiated nuclei (megaloblasts), known as megaloblastic anemia.

Inadequate dietary intake and poor absorption (50%) of folic acid results in its deficiency amongst the population. However, a study conducted amongst Indian adolescents reported no association between folate intake and RBC folate deficiency or between anemia status and RBC folate deficiency. This is possibly due to high loss of folate of around 33% during cooking. Whereas, vitamin B₁₂ deficiency is the result of either a direct nutritional deficiency (common in vegans) or malabsorption due to the absence of either gastric acid or intrinsic factor needed for absorption.

Vitamin B₁₂ deficiency, in particular, leads to pernicious anemia (megaloblastic macrocytic anemia), which is a specific autoimmune disease that reduces or eventually eliminates the active absorption of vitamin B₁₂ from the diet. Studies have suggested that anemia does not usually appear until an individual has a relatively severe state of depletion of the vitamin B₁₂.

High prevalence of folate or vitamin B₁₂ deficiency has been reported across different age groups in different parts of the world. The CNNS reported that 37% adolescents were deficient in folate and 31% had vitamin B₁₂ deficiency. The survey documented that 25.6% adolescents had anemia related to folate or vitamin B₁₂ deficiency as defined by deficient hemoglobin, folate and vitamin B₁₂ and sufficient ferritin levels.

2.1.3 Vitamin A

The role of vitamin A in iron metabolism was recognized already in the 1980’s, when studies showed that the effect of iron supplementation on hemoglobin concentrations could be enhanced by the addition of vitamin A. The mechanisms by which vitamin A enhances hemoglobin formation are not completely understood, but vitamin A is suggested to directly regulate erythropoiesis through effects on transferrin receptors affecting the utilization and mobilization of tissue iron stores. It may also cause anemia through indirect effects, such as decreasing the iron available to produce red blood cells, stimulating erythroid precursors in the bone marrow, decreasing iron absorption, or increased susceptibility and severity of infections.

Subsequent studies have documented a significant increase in the levels of hemoglobin, hematocrit and plasma iron following supplementation of vitamin A.

The CNNS reported that 16% of the adolescents have vitamin A deficiency. A study conducted in Vietnam documented that subjects with vitamin A deficiency as defined by RBP <1.05 had 2.9 times higher risk of developing iron deficiency (p<0.001). Earlier studies have also
shown significant correlation between hemoglobin, serum ferritin and vitamin A \(^{101-103}\). Studies conducted amongst children have reported that the proportion of vitamin A deficiency was higher amongst anemic children as compared to children with no anemia, suggesting a role of vitamin A in anemia \(^{104-106}\).

### 2.1.4 Riboflavin

Riboflavin has an important role in erythropoiesis, probably by altering iron metabolism in liver and its deficiency may cause anemia \(^{71,107}\). In addition, riboflavin deficiency may also exacerbate iron deficiency by increasing intestinal iron loss, reducing iron absorption and increasing crypt cell proliferation \(^{77,108,109}\). Deficiency may impair the synthesis of globin, and reduce the activity of NADH-FMN oxidoreductase so that iron becomes trapped in ferritin. It is theoretically possible that riboflavin deficiency in conditions with increased oxidant stress may also lead to hemolytic anemia \(^{70}\).

Earlier studies have documented beneficial effect of riboflavin supplementation on improvement in hematological status alone or combined with iron in deficient populations \(^{77,108,110,111}\). Contrary to these studies, a study conducted in Coˆte d’Ivoire showed lower odds of anemia for women of reproductive age with riboflavin deficiency \((p<0.05)\) \(^{112}\). Erythrocyte glutathione reductase activation coefficient deficiency was also reported to be inversely related to the risk of anemia \((p<0.05)\) \(^{103}\).

### 2.1.5 Vitamin D

Various mechanisms have been suggested to explain the association of Vitamin D deficiency (VDD) with anemia. VDD leads to decreased calcitriol production in bone marrow and increased membrane permeability of calcium, resulting in impaired erythropoiesis \(^{78,113}\). VDD leads to hyperparathyroidism which raises proliferation of erythroid progenitor cells \(^{114}\). Another possible mechanism is the role of VDD with higher hepcidin level in the body, resulting in anemia \(^{115}\).

The CNNS reports that 23.9% of the adolescents are deficient in vitamin D \(^{1}\). Low 25OHD levels were found to be associated with increased risk of anemia in a nationally representative sample of community-dwelling individuals \(^{116}\). A recent cross sectional study conducted amongst school children showed that children with a VDD were almost 3.45 times more likely to be anemic compared with children with sufficient vitamin D status \(^{117}\). They reported that the increased risk of anemia was found to increase significantly at 25(OH)D level of \(< 44 \text{nmol/L} \ (17.6 \text{ng/mL})\). Other studies have also reported association of VDD with anemia \(^{114,115,118,119}\).

### 2.1.6. Zinc and Copper

Zinc is usually not one of the nutrients associated with anemia, although evidence suggest that zinc deficiency might increase oxidative stress particularly in initiation of superoxide anion radicals and thereby reduce the lifespan of the erythrocyte, causing anemia \(^{71,106}\). Another mechanism through which zinc deficiency might affect the hemoglobin synthesis is lower erythropoietin concentrations \(^{71,106}\). In addition, zinc is a catalyst for many enzymes that are needed for red blood cell production; as a result, a zinc deficiency may be associated with anemia \(^{71,120}\). The CNNS reports that 31.7% adolescents were deficient in zinc \(^{1}\).

Copper is an essential element which is required for conversion and maintenance of iron in Fe\(^{3+}\) state for its subsequent absorption and utilization \(^{70,71}\). Dietary copper deficit and genetic defects of copper metabolism may significantly affect the iron metabolism and red cell resistance to oxidative stress, and thus may contribute to the burden of anemia \(^{70,71}\). In addition, copper is also associated with impaired host defenses and could increase the burden of anemia secondary to infection. Copper
excess may also contribute to anemia by inducing hemolysis. Zinc and copper have an antagonistic interaction within the erythrocyte. It has also been demonstrated that large doses of zinc inhibit the copper absorption and may produce copper deficit. This may indirectly affect the iron status by interference with iron mobilization and impaired immune responses leading to anemia.

A study conducted amongst Sri Lankan preschool children showed a significant correlation between serum zinc and hemoglobin levels. Wieringa et al. (2014) reported that prevalence of zinc deficiency was higher amongst anemic children (39.6 vs. 24.8) and anemic women (30.4 vs. 24.8) as compared to subjects with no anemia. They suggested a possible role of zinc deficiency on hemoglobin status.

On the other hand, inhibitory effect of zinc on iron absorption has been proposed as they compete for a shared absorptive pathway. A large multicounty trial documented that zinc supplementation had a significant negative effect on hemoglobin concentrations (-2.5 g/L) amongst infants. However, combined supplementation of iron and zinc was more effective and safer in reducing anemia in deficient populations.

2.2 Infection and inflammation

2.2.1. Soil-transmitted helminthes

Approximately one third of the world's population is infected with helminths. Human intestinal helminthiasis is most commonly caused by Soil-transmitted helminthes (STHs), roundworms (Ascaris lumbricoides); hookworms (Necator americanus and Ancylostoma duodenale); and whipworm (Trichuris trichiura). Scientific evidence suggests that in areas with high prevalence of helminthiasis (50-80%) a significant association exists with anemia prevalence.

Observational data suggest an inverse relation between intestinal helminthiasis and haemoglobin concentrations. Anemia from STH infections is caused by multiple mechanisms: i) blood loss in the gastrointestinal system ii) malabsorption of hemo poetic nutrients such as iron, vitamin B, folic acid, vitamin C, vitamin A, iii) suppression of appetite, and iv) general inflammation.

Hookworm, due to the high levels of intestinal blood loss, is likely the main STH contributing to anemia. There is no national database on the prevalence of soil transmitted helminthes (STH) infestation in India or estimates of its contribution to anemia in children. More than one third of Indian adolescents had a history of infestation. Each hookworm ranges in length from 5 to 13 mm and causes up to 0.3 ml of blood loss per day from the intestinal mucosa. A blood loss of 1 ml per day (equivalent to 0.347 mg of iron at a hemoglobin level of 100 g/litre of blood) would cause a loss of 250 mg of iron in 2 years, or the equivalent of the total body iron stores in a woman of 50 kg. Over a period, even small hookworm loads may cause sufficient blood loss to deplete body iron reserves. Depending on the status of host iron, a hookworm burden (i.e., the intensity of infection, or number of worms per person) of 40 to 160 worms is associated with hemoglobin levels below 11 g per deciliter. Heavily infected patients are simply unable to maintain adequate iron stores and become anemic. Systematic review of 12 studies of deworming during pregnancy showed that women with light hookworm infection (1–1999 eggs per g of faeces) had a standardized mean difference of hemoglobin that was 0.24 g/L lower (95% CI -0.36 to -0.13) than in those with no hookworm. Children have an estimated loss of iron equal to twice the amount of their daily iron requirement. Poor growth rate are frequently observed in children with STH infection.

Studies conducted in areas with a high prevalence of STH infestation of 30-80% showed significant association with the
prevalence of anemia amongst adolescents^126–128^. A study reported that the prevalence of anemia was double in girls infected with STH (53.6%) compared to those who were not reported to be infected (25%). However, another study conducted in Delhi showed no such association^127^. A study conducted in Vietnam documented that women of reproductive age have 1.3 times higher risk of developing iron deficiency due to hookworm infection^101^.

The authors reported that hookworm infection was negatively correlated with hemoglobin (p<0.05), serum ferritin (p<0.001) and serum RBP levels (p<0.05). A meta-analysis of 14 randomized controlled trials of deworming in sub-Saharan Africa and Asia showed a significant increase in mean hemoglobin (1.71 g/L, 95% CI: 0.70–2.73), with an increased response in those provided with iron supplementation^125^. This could translate on a public health scale into a small (5% to 10%) reduction in the prevalence of anemia in populations with a relatively high prevalence of intestinal helminthiasis.

A recent Cochrane review reported no benefit of deworming on hemoglobin levels amongst school children^134^.

However, the evidence used for the analysis was of low quality, due to problems with trial methods and inconsistency between results of different studies. Beneficial effect of deworming was reported by a systematic review which documented that routine administration of intestinal anthelmintic drugs resulted in a marginal increase in hemoglobin (1.71 g/l)^125^.

These results can translate on a public health scale into 5-10% reduction in the prevalence of anemia in populations with a relatively high prevalence of intestinal STH.

2.2.2. Helicobacter Pylori (H. Pylori)

Helicobacter pylori is a gram-negative bacillus and the commonest bacterial pathogens in human and is transmitted primarily via fecal-oral, gastric-oral or oral-oral routes^135^.

At least half of the world’s populations are infected by Helicobacter pylori^136^.

Prevalence of H. pylori infection among developing country populations is high, ranging between 50-90%,^137^ and has been implicated in the etiology of gastric and duodenal ulcer and other morbidities^138–140^. H. pylori infection is very common in Indian children (87%) especially in low socioeconomic status. The prevalence studies from Hyderabad and Mumbai have shown that by 10 years of age more than 50% and by 20 years more than 80% of population is infected with H. pylori^141,142^.

Another study from Bangalore has detected H. pylori infection in 82% of 50 children (6 to 18 years of age) by 13C urea breath test^143^.

Most infected children remain asymptomatic throughout their childhood and only a small fraction develops peptic ulcer disease as young adults^131,142,144^.

The biological mechanism explaining the relationship between H. pylori bacterial infection and decreased iron stores is not fully understood. The postulated mechanisms of H. pylori infection in causation of anemia are: i) hemorrhagic lesions in the stomach or duodenum, ii) poor absorption of iron due to low gastric acid secretion and iii) consumption of iron by the bacteria itself^141,142,145^.

H. pylori infection can cause hemorrhagic lesions in the stomach or duodenum leading to a negative effect on body iron balance by chronic blood loss from the gastrointestinal tract^146,147^. H. pylori bacteria may also lead to IDA by sequestering and utilizing iron, thus competing with the human host^146,147^.

Few studies have suggested that H. pylori causes iron deficiency anemia especially in adolescent girls without producing any hemorrhagic lesions in the stomach or duodenum^148–150^. Another explanation for a relationship between H. pylori infection and IDA involves the possible effect of H. pylori gastritis on gastric acid secretion and iron absorption^147,151^.

H. pylori was significantly more frequent in children with
hypochlorhydria (pH> 4) compared with those with gastric juice pH ≤4.

Sarker et al. (2004) showed that gastric acid secretion is significantly reduced in H. pylori-infected anemic young children and its eradication restores gastric acid secretion 152. However, a recent study has reported contradicting evidence suggesting that H. pylori infection is not associated with hemoglobin, serum ferritin, body iron and vitamin B_{12} concentrations amongst Indian children 153. More studies need to be undertaken to conclusively confirm its association with anemia.

2.2.3. Malaria

Approximately 30% of the world’s population is exposed to malaria. Malaria causes between 1 million and 3 million deaths every year. Plasmodium falciparum is the most pathogenic species and can lead to severe anemia, and subsequent hypoxia and congestive heart failure.

Malaria related anemia is caused by increased erythrocyte destruction (excess removal of non-parasitized erythrocytes in addition to immune destruction of parasitized red cells), decreased erythrocyte production (impaired compensation for this loss by bone marrow dysfunction), general inflammation, reduced intestinal iron absorption, sequestration of iron within the malarial pigment hemeozoin, mobilization of iron to body stores and release of iron into the circulation during intravascular hemolysis 154,155. Anemia due to Plasmodium falciparum infection is a major health problem in endemic areas for young children and pregnant women.

A meta-analysis showed that presence of malarial parasite was associated with 1.5 times higher risk of anemia 156. However, the odds of anemia were 2.9 times higher in individuals with combined malaria and STH infection 156. Another meta-analysis in non-pregnant populations showed co-administration of praziquantel together with albendazole to target other parasites, increased mean hemoglobin by 2.37 g/L 131.

The interaction between malaria and iron and folate supplementation has been the subject of intense research and controversy in recent years 157 by the results of two cluster-randomised double-blind intervention trials of iron and folate in preschool children in Zanzibar and Nepal 158,159. In Zanzibar, an area of high P falciparum endemicity, the increased risk of severe morbidity and mortality in children receiving iron and folate supplementation was shown to outweigh the benefits 159.

The subsequent WHO led Expert Consultation emphasized the need to exercise caution against universal iron supplementation for children younger than 2 years in malaria-endemic regions where appropriate screening and clinical care are scarce 160. Subsequently, a systematic review of 68 randomized and cluster-randomized trials covering 42,981 children did not identify any adverse effect of iron supplementation on risk of clinical malaria or death, in both anemic and non-anemic children, in malaria-endemic areas 160. However, this finding relates to settings in which there are adequate regular malaria surveillance and treatment services in place, which might not be the case in many low-resource settings. Thus, treatment of children with iron supplements should be accompanied by adequate screening for and treatment of malaria.

2.2.4. HIV/AIDS

Anemia is the most common hematological complication associated with HIV infection, and is a marker of disease progression and survival 161. The mechanism of HIV/AIDS-related anemia is multifactorial, resulting from HIV infection and the induced anemia of chronic disease, AIDS-related illnesses, and antiretroviral treatment 162. An obvious cause of anemia in patients with HIV infection is blood loss. Other than blood loss, the pathophysiology of HIV-associated anemia may involve 3 basic mechanisms: decreased RBC production, increased RBC
destruction, and ineffective RBC production.

2.2.5. Acute and Chronic Inflammation

Infection leads to inflammation leading to decrease the plasma concentrations of several nutrients. Upon infection and inflammation, iron is sequestered in the macrophages and hepatocytes and iron absorption decreases, thus limiting iron to the invading pathogen. This also results in restricted erythropoiesis and lowered hemoglobin concentrations.

Inflammation-associated anemia is generally due to the known pathway of hepcidin-induced regulation of Fe homoeostasis. Hepcidin is a 25 amino acid hepatocyte-derived peptide and controls movement of iron into plasma by regulating the activity of the sole known iron exporter ferroportin-1. Down-regulation of the ferroportin-1 exporter results in sequestration of iron within intestinal enterocytes, hepatocytes, and iron-storing macrophages, reducing iron bioavailability. Urinary and serum hepcidin can be increased to up to 100-fold during infections and inflammation causing a decrease in serum iron levels. Its expression is also increased by higher body iron levels or iron overload and decreased by anemia and hypoxia. Thus, hepcidin is now considered as the iron hormone, since it is modulated by iron concentration in the body.

In a study conducted on anemic women reported that C-reactive protein concentrations were notably high in 54% of the anemic women with no nutritional deficiencies suggesting the role of inflammation in anemia amongst them. Another study conducted by Pasricha et al. (2010) in India showed that inflammation as defined by CRP >5 mg/L was higher in anemic infants as compared to non-anemic. They also reported that higher CRP was significantly associated with lower hemoglobin status. Similarly, a study conducted amongst Cambodian children reported significant association of AGP with decreasing Hemoglobin and increasing ferritin levels.

2.3. Hemoglobinopathies

Inherited genetic hemoglobin disorders, such as sickle cell trait or thalassaemias, are one of the top three causes of anemia globally. Hemoglobinopathies can be categorized under: (1) sickle cell disorders (SS, SC, S/β thalassaemia), (2) β thalassaemias (homozygous β thalassaemia, Hb E/β thalassaemia), (3) α thalassaemias/haemoglobin H disease (homozygous αthalassaemia, α/α thalassaemia), and (4) harmless combinations (CC, C/β thalassaemia, EE, DD, D/β thalassaemia, etc). Genetic red blood cell disorders such as thalassemias and thalassemia trait, sickle cell disorders and sickle cell trait (Hb S variants), glucose-6-phosphate deficiency (G6PD), other hemoglobinopathies and hemolytic anemia, and Krüppel-like factor 1 variants, result in abnormalities in the function, structure, or production of red blood cells causing anemia. By different mechanisms, sickle cell disease, hemolytic anemias, and G6PD deficiency increase the destruction of red blood cells; while the thalassemias produce ineffective red blood cells, as well as a shorter red blood cell lifespan.

Roughly 5% of the global population is estimated to carry a significant hemoglobin variant. A study conducted amongst 11,090 school children residing in two states of the India reported prevalence of β-thalassemia trait to be 4.05% (Delhi: 5.5%, Mumbai: 2.7%). The prevalence of Hb-D (0.9%), Hb-S trait (0.1%), β Thal (0.2%) and HbE trait (0.02%) was found to be low amongst adolescents. They reported that prevalence of anemia was significantly higher (75.5% (Delhi: 60.5%, Mumbai: 90.8%)) amongst children with β-thalassemia trait as compared to children with no hemoglobinopathy (22.7% (Delhi: 15.8%, Mumbai: 29.6%)). A study conducted in anemic Cambodian children (80.9%) and women (70.9%) reported...
higher prevalence of hemoglobinopathies as compared to non-anemics (68.2%)\(^{106}\). They reported that individual with hemoglobinopathies had a 1.5 times higher risk of anemia and suggested genetic hemoglobin disorders as major predictors of anemia rather than iron deficiency. Another study conducted in Kenya have also shown similar associations with anemia \(^{178}\).

Both sickle cell disease and hemoglobinopathies are associated with ineffective erythropoiesis that stimulates an increase in iron absorption even when iron stores are adequate, resulting in elevated levels of sTfR and ferritin \(^{179}\). Individuals with hemoglobinopathies have low iron deficiency but high anemia status. Simultaneously, mild to severe anemia may occur depending on whether the Hb variants are homo- or heterozygous, as a result of the negative impact on Hb concentrations. Hence, both genetic Hb disorders and a genetic enzyme deficiency have the potential to confound the diagnostic accuracy of ferritin, sTfR and Hb \(^{180,181}\).

### 2.4. Other Factors

#### 2.4.1. Overweight and obesity

Overweight and obese children have been reported to have elevated hepcidin levels and poorer iron status possibly due to subclinical inflammation as compared to normal weight children, despite having similar dietary iron intake to normal-weight children \(^{182}\). Although obesity is associated with iron deficiency, hemoglobin concentrations generally tend to be within the normal range \(^{183,184}\). The link between weight gain and iron status is still not completely understood.

#### 2.4.2. Environmental enteropathy

Environmental enteropathy defined as a state of chronic intestinal inflammation, without obvious diarrhea results in a chronic state of inflammation. It occurs in individuals exposed to long-term poor water, sanitation and hygiene and repeated exposure to environmental pathogens especially populations belonging to low income settings \(^{185-189}\).

Researchers have suggested that environmental enteropathy may be an important cause for failure of nutritional interventions in low income countries \(^{188}\).

### 2.5 Deficiency of Iron in Indian Soil

Soil deficient in iron leads to poor iron contents of foods grown on it. A study conducted by the Indian Institute of Soil Science, Indian Council of Agricultural Research, India found that the soils of as many as 174 districts across 13 states in India were deficient in iron, manganese and copper. The iron, manganese and copper were deficient by 12.9%, 6% and 4.3% of soil samples, respectively \(^{190}\).

The recently released Indian Food Composition Tables by National Institute of Nutrition, Hyderabad have revealed lower iron content in food stuffs especially in food stuffs previously thought to be rich in iron such as rice flakes, mustard leaves, bathua leaves over the past decade \(^{191}\).

### 2.6 Adolescent Pregnancy

Pregnancy during adolescence increases the demand for iron and aggravates iron deficiency and IDA. The growing pregnant adolescents compete for the nutrients with the growing foetus. Recent NFHS-4 survey in India documented that 27% of girls are married before 18 years of age and 8% of the girls in the age group of 15-18 years were pregnant \(^{192}\). The incidence of anemia has been reported to be lower among adolescent girls who were currently unmarried as compared to their married counterpart \(^{5}\). Poor pregnancy outcomes such as prematurity, total growth retardation, increased risk of preterm labor, low birth weight \(^{193}\), and child and maternal mortality \(^{194,195}\) increases in anemic adolescent mothers.

### CONCLUSION

India is lagging behind in achieving the World Health Assembly targets for anemia reduction by 2025 \(^{196}\). Anemia Mukt
Bharat strategy launched in 2018 is targeting iron and folic acid supplementation to adolescent girls as they provide the second window of opportunity to eliminate or reduce the burden and break the intergenerational cycle of anemia before entering into the pregnancy. However, efforts are needed to strengthen the supply chain mechanism for IFA and achieve effective program implementation through periodic trainings at all levels. Provision of IFA supplementation as the main intervention for the management of anaemia may benefit 50% of the anemic adolescents and prevent anemia in normal adolescents. Anemia will not be addressed by IFA programme alone or through improving dietary intakes. Disjointed efforts of the various agencies to address anemia, underfunding, poor program implementation, inadequate counseling and low visibility of national anemia control programme may have led to the failure in effectively addressing anemia amongst school age children.

Only prophylaxis dose of iron is being provided when more than 70% require treatment doses. Hence, a drastic reduction in the prevalence of anemia cannot be expected. There is also a lack of scientific evidence on successful intervention models for treatment of anemia.

Effective convergence of several governmental departments like health, education, water supply and sanitation is needed. Promotion of adequate WASH practices, adoption of toilets and control of diarrhea through use of oral rehydration solution (ORS) along with zinc supplementation needs to be promoted for reducing the prevalence of anemia due to chronic inflammation and EE. Therefore, more studies need to be undertaken to understand the determinants of anemia amongst adolescents in India which will help in addressing the burgeoning problem of anemia amongst them.

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