FOGSI General Clinical Practice Recommendations

Management of Iron Deficiency Anemia in Adolescent Girls

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Introduction and rationale

Anemia among adolescent girls and pregnant women is a major health concern worldwide. Studies show that approximately 1.72 billion people suffer from anemia globally (1). According to a World Health Organization (WHO) estimate, about 50% of the cases of anemia can be attributed to iron deficiency (ID) (2).

Iron deficiency anemia (IDA) is the most advanced stage of ID that has an adverse health impact on adolescents. Adolescents (age 10-19 years) are vulnerable to IDA due to increased iron demand in order to meet the expeditious growth. Moreover, menstruation increases the risk for IDA in adolescence girls (3). Low dietary intake of iron further contributes to the risk of IDA (4, 5). Numerous studies in India have shown high rates of infection and worm infestation as the significant determinants of anemia (6-8). The social norm of early marriage and consequent adolescent pregnancy contribute to increasing prevalence of adolescent anemia. Iron deficiency has been associated with menstrual disorders and stunted physical growth (9, 10). It has been found to reduce physical work capacity and cognitive functions which in turn affect learning and scholastic performance (11). Cell-mediated immunity, which has been shown to decrease in children with IDA, improves with iron supplementation (12, 13).

The prevalence of IDA is higher in developing countries (30-48%) than developed nations (4.3-20%) (14). Moreover, developing countries have a higher incidence of anemia among adolescent girls than their male counterparts (15). A situational analysis by WHO in South East Asian countries reported the prevalence of IDA to be 56-90% (16). Concerned about the high prevalence, Government of India has undertaken a number of national surveys to understand the pattern of prevalence of anemia across the country in the local context as shown in Table 1 (17). About 72-80% younger (12-14 years) adolescents and 73-84% older adolescents (15-17 years) were found to have IDA in a micronutrient survey conducted by the National Nutrition Monitoring Bureau (NNMB, 2003) (18). Subsequent to these surveys, a study by Indian Statistical Institute in 2009 including 177,670 adolescent girls from 35 states or union territories of India, found 89.7% adolescent girls to be suffering from anemia (19).

Table 1. Prevalence of anemia in adolescent girls in India

Survey	**Adolescent anemia (%)**
National Family Health Survey NFHS-2 (1998-99) (20)	61
National Family Health Survey NFHS-3 (2005-2006) (21)	56
The District Level Household Survey-2 (DLHS-2, 2002-2004) (17)	97.6
National Nutrition Monitoring Bureau (NNMB, 2003) (18)	72-80: 12-14 years 73-84: 15-17 years
Indian Statistical Institute in 2009 (19)	89.7

The cost of therapeutic measures by both public and private sectors, the loss of productivity as a result of increased maternal mortality, and probable long-term negative implications of impaired mental development on human capital formation impede the economic development of the country (22). The loss as a consequence of IDA cost up to 4.05% of gross domestic product (GDP) in developing countries, and 1.18% of GDP in India (23).

Several government programs have been planned and executed to combat the high rate of IDA. National Nutritional Anemia Prophylaxis Program, 1970; National Anemia Control Program, 1991; and 12/12 initiative, 2007 are a few of the national drives undertaken by the government of India. Despite these efforts, the adolescent anemia rate is still high, and thus, appropriate actions for prevention and management of anemia are crucial to strengthening the health economy of India. Moreover, WHO Global Nutrition Targets 2025, Anemia Policy Brief aims at targeting 50% reduction of anemia in women of reproductive age (24).

National guidelines and standards of care for anemia in adolescents are, in practice, in many countries to improve the outcome of treatment (25-28). However, the practice remains less satisfactory in India, which might partly be due to diverse religions, food habits, lifestyles, languages, cultures, and traditions that influence management practices. Hence, a need for country-specific harmonized guideline addressing the needs of Indian patients was observed parallel to recommendations by the WHO. It is expected that the current document developed by the Federation of Obstetrician and Gynecology Society of India (FOGSI), would promote a standard of care considering the economic disparity in a limited resource setting like India.

Methodology

The current Good Clinical Practice Recommendations (GCPR) from the FOGSI for the adolescent anemia are developed by ‘Expert panel’ from across the nation with huge experience in managing patients with anemia. A group of panel members reviewed the literature and collected the evidence. A literature search was carried out electronically in the medical search engine ‘PubMed’ and Google Scholar for relevant reports. The main search strategy included keywords: adolescent anemia with no limitation of time. Further, the section headers in the current document were used as keywords along with the main keywords. Specific evidence from India (MedIND/IndMED) was identified. Also, a manual search was conducted in key non-indexed journals. Only abstracts written in English were included. Evidence from randomized clinical trials (RCTs) and non-RCTs conducted in India and abroad were considered in framing the GCPR. Existing recommendations from national and international guidelines for the management of anemia were also noted.

The draft guideline, with proposed GCPR was reviewed by the expert panel members through mail communications followed by meetings to arrive at a consensus on each GCPR for the management of adolescence anemia. Areas where evidence is weak or does not exist, the consensus opinion of the expert panel has been relied upon. For classifying the quality of evidence as 1, 2, 3, or practice point, the modified grade system was used (Table 2) (29). Grade A recommendations in the guidelines should be interpreted as "recommended" and the grade B recommendations as "suggested".

Table 2. Grading of recommendations

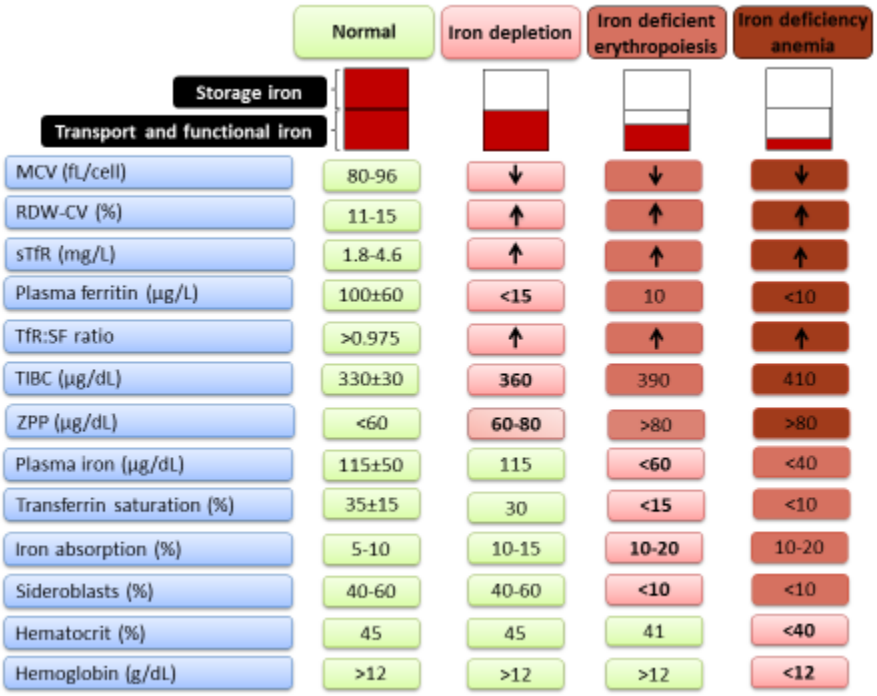
Grading of recommendations	
GRADE A	Strongly recommended “RECOMMENDED”
GRADE B	Weaker recommendation “SUGGESTED”
Classification of level of evidence	
1	High-quality evidence backed by consistent results from well-performed randomized controlled trials or overwhelming evidence from well executed observational studies with strong effects
2	Moderate quality evidence from randomized trials
3	Low-quality evidence from observational evidence or from controlled trials with several serious limitations
4 (Practice point)	Not backed by sufficient evidence; however, consensus reached by expert panel group based on clinical experience and expertise

Diagnosis

The etiology of anemia is multifactorial and needs effective intervention to be practiced. Other causes of anemia are underestimated, hence, it requires right indicator to monitor the impact of intervention. Recent recognition of general and potentially serious negative effects of ID (9-13), has made the diagnosis of ID as important as diagnosing persons with IDA.

Iron deficiency anemia progress in three phases. In the first phase, the depletion of stored iron (stage I) occurs but hemoglobin (Hb) synthesis and red cell indices remain unaffected. In the subsequent stage II, the bone marrow supply of iron is reduced. Finally, in stage III the iron supply will be insufficient to maintain a normal Hb concentration, called IDA. Different phases of iron deficiency (ID) are as presented in Figure 1.

Figure 1. Various stages of iron deficiency and their indicators (30)



Overall, the diagnosis is based on two different aspects, first, a clinical presentation including a complete history of the patient, possible signs and symptoms, along with a detailed physical examination; and second the laboratory tests (14).

Evidence

Clinical presentation

A primary diagnosis includes identifying the possible signs and symptoms and taking a complete patient history. Symptoms rely greatly on the speed of onset of anemia, its severity, and the patient characteristics. Individual with ID (stages 1 and 2) may experience no symptoms or symptoms common to all anemia that includes general weakness, irritability, fatigue, headache, poor concentration, and intolerance to exercise (31). Some iron deficient patients, with or without anemia, might have atrophy of lingual papillae, alopecia, or dry mouth due to loss of salivation (32). The symptoms specific to the IDA (stage 3) include; the syndromes of Plummer-Vinson or Paterson-Kelly (dysphagia with esophageal membrane and atrophic glossitis), gastric atrophy, stomatitis due to the rapid turning over of epithelial cells (33); spoon-shaped fingernails (koilonychia), and chlorosis. These changes are caused by the reduction of iron-containing

enzymes in the epithelia and the gastrointestinal (GI) tract (32). Pica, the eating disorder in which there is a tempting desire to eat non-nutritive and unusual substances, such as gypsum, chalk, soil, ice (pagophagia) or paper, might appear in some cases. Pagophagia is quite specific to ID and responds quickly to treatment (34). Physical examination might be normal or show pallor of varied intensity (32).

Laboratory tests

There are four classes of tests available for assessment of ID.

- First, hemogram based methods: Hemoglobin (Hb), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean cell hemoglobin concentration (MCHC), red cell distribution width (RDW), reticulocyte Hb content, % hypochromic cells, red cell size factor, and low Hb density.
- Second, direct measurement of iron stores: serum iron (Fe), total iron binding capacity (TIBC), serum ferritin and bone marrow biopsy.
- Third, assessment of iron incorporation into heme (absorption): free erythrocyte protoporphyrin (EPP).
- Fourth, assessment of iron uptake: soluble serum transferrin receptor (sTfR), soluble transferrin receptor-log [ferritin] (sTfR-F) index, and zinc protoporphyrin (ZPP).

Red blood cell parameters and indices

A primary step in the diagnosis of IDA is to consider the complete blood count, which is simple, inexpensive, rapid to perform and helpful for early prediction of IDA. Complete blood count (CBC) includes Hb, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Changes in Hb concentration and hematocrit occur (as shown in Figure 1) only in late stages; both these tests are late indicators of ID. Nevertheless, these tests are important for determining IDA. Low Hb with a reduced MCV is usually the initial finding on a routine CBC. The severity of anemia is based on the patient's Hb/hematocrit level. Altitude above sea level and smoking are the known modifiers of Hb concentration (35). Standard anemia cut-offs may underestimate anemia if these factors are ignored. World Health Organization recommends adjustments to be

made to the measured Hb concentration among persons living at high altitudes, and in smokers as depicted in Table 3 and Table 4. Hemoglobin concentration is the commonest hematological estimation, there is a strong correlation between Hb concentration and serum ferritin levels (36). Generally recommended methods are cyanmethemoglobin and the HemoCue® system (37).

Table 3. Altitude adjustments to measured hemoglobin concentrations (Adapted from WHO) (37)

Altitude (Meters above sea level)	**Measured Hemoglobin adjustment (g/dL)**
<1000	0
1000	-0.2
1500	-0.5
2000	-0.8
2500	-1.3
3000	-1.9
3500	-2.7
4000	-3.5
4500	-4.5

Table 4. Adjustments to measured hemoglobin concentrations for smokers (Adapted from WHO and INACG) (37, 38)

Smoking status	**Measured hemoglobin adjustment (g/dL)**
Non Smoker	0
Smoker (all)	-0.3
½-1packet/day	-0.3
1-2 packets/day	-0.5
≥2 packets/day	-0.7

Mean corpuscular volume is the measure of the average red blood cell volume, and MCHC is the measure of the concentration of Hb in a given volume of packed red blood cells. It is important

to note that up to 40% of patients with true IDA would have normocytic erythrocytes (i.e. a normal MCV does not rule out IDA) (32).

Red cell distribution width (RDW) is a measure of the change in red blood cell width and is used in combination with the MCV to distinguish an anemia of mixed cause from that of a single cause. Increased RDW represents variance in the red blood cell volume distribution, similar to a peripheral blood smear anisocytosis. In the initial stages of IDA, there is a fall in MCV accompanied with increasing RDW values due to a preponderance of microcytes (39, 40). Following treatment, marked reticulocytosis occurs in the first 4 weeks, manifested as a sudden increase in RDW, sometimes to over 30% (41). Thus, falling MCV accompanied by an elevating RDW should alert the clinician to the presence of possible IDA which is then confirmed by marked RDW increase occurring after the initiation of therapy (42). It is important to note that RDW may be elevated in the early stages of IDA or when a patient has both folate with or without vitamin B12 deficiencies and IDA, both produce macrocytic anemia (43). RDW has been shown to have a better sensitivity than MCV for the diagnosis of IDA (44). There are few studies from India which correlate red cell indices with ferritin. It has been suggested to include RDW in routine CBC report as an effective tool for the diagnosis of IDA in early stages in order to reduce the need for iron status markers (45-49).

It is common for the platelet count to be greater than 450,000/µL in the presence of IDA, though, the red cell count falls. It is important to note that microcytosis visible on the peripheral smear may be seen even before abnormalities in CBC develop. If the patient has coexistent folate and or vitamin B12 deficiency, the peripheral smear would show a mixture of macrocytic and microcytic hypochromic erythrocytes, along with normal MCV (42). Furthermore, the presence of microcytic hypochromic red cells and characteristic “photo pencil cells” are indicative of IDA (50).

Differential diagnosis: Iron deficiency anemia is characterized by microcytic red blood cells. Other conditions causing microcytic RBCs include anemia of chronic disorders, beta-thalassemia, and sideroblastic anemias. All the tests described above helps differential diagnosis of various microcytic RBCs etiologies as shown in Table 5. However, in low-resource settings like India, where these tests are not easily available, the RBC indices are of great value for primary diagnosis which can reduce unnecessary investigative costs. Of all available indices, the

Meltzer index (MCV/RBC) has been shown as the most reliable index with high sensitivity (51, 52).

Table 5. Differential diagnosis of various microcytic RBCs etiologies (53-55)

Indicator	**IDA**	**BT**	**SA**	**ACI**
Hemoglobin	Decreased	Normal or decreased	-	Decreased
Ferritin	Decreased	Normal Increased	Normal or increased	Normal or Increased
Serum iron	Decreased	Normal or increased	Normal or increased	Normal or Decreased
TIBC	Increased	Normal	Normal	Slightly decreased
TS	Decreased	Normal to increased	Normal to increased	Normal to slightly decreased
sTfR	Increased in severe IDA	>100 mg/L	-	Normal
FEP	Increased	Normal	-	Increased
MCV	Decreased	Decreased	Normal	Normal or decreased
RDW	Increased	Normal to increased	Increased	Normal
Reticulocytes	Decreased Increased	_ Decreased	- -	Normal or decreased -

ACI, acute chronic inflammation; BT, beta-thalassemia; IDA, Iron deficiency anemia; FEP, free erythrocyte protoporphyrin; MCV, mean corpuscular volume; RDW, red cell distribution width; SA, sideroblastic anemia; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TS,transferrin saturation

Serum Ferritin

Serum ferritin is one of the best indicators to assess ID. Every 1 μg/L of serum ferritin corresponds to 8-10 mg storage of iron. Guyatt et al, have reported likelihood ratio (LR) for the presence of IDA in relation to positive serum ferritin levels. On the basis of these data, a serum ferritin ≤15 μg/L confirms ID, and a serum ferritin ≥100 μg/L rules out ID (56). Serum ferritin is an acute-phase reactant that may be falsely elevated in the setting of infection, chronic inflammation, chronic renal failure, and malignancy. However, the sensitivity and specificity of the serum ferritin are little changed if the 100 μg/L threshold is used (57).

Serum Iron and total iron binding capacity

Serum iron and TIBC are the other independent indicators of iron stores or availability. The TIBC measures the obtainability of iron-binding sites. Extracellular iron is transported in the body bound to a specific carrier protein, transferrin. Hence, TIBC indirectly measures transferrin levels, which increase as serum iron concentration (and stored iron) decreases. The TIBC decreases with malnutrition, inflammation, chronic infection, and cancer, hence, it has poor sensitivity and specificity for the diagnosis of IDA (58).

Zinc protoporphyrin (ZPP)

The erythrocyte zinc protoporphyrin is formed when zinc is incorporated into protoporphyrin in place of iron during the biosynthesis of heme. Short supply of iron as in IDA increases ZPP production and elevates ZPP/heme ratio whereas in normal condition the reaction of ZPP with iron predominates (58) . Before the onset of anemia, ZPP/heme reflects iron status and detects iron deficiency. This test is most accurately reported as the ZPP or ZPP/heme ratio. It is a sensitive test, but with limited specificity because ZPP increases in the settings of inflammation, lead poisoning, anemia in chronic disease (ACD), and hemoglobinopathies (59).

Soluble transferrin receptor (sTFR)

Soluble transferrin receptor is expressed on erythrocyte membranes which transports circulating transferrin bound iron into the cell. In iron deficiency these cells over express the sTfR and consequently increasing concentrations of sTfR is detected in blood circulation. Thus the concentrations of soluble trasnferrin receptor and serum ferritn are reciprocally related. . Though it is a sensitive measure of tissue iron supply the assay is being globally standardized (60). At present the cutoffs of sTfR depend on the assay used, which is a key limitation. Currently the use of sTfR to ferritin ratio and sTfR to log ferritin index have been recommend and are used for defining iron deficiency and effectiveness of intervention in a population.

Reticulocyte hemoglobin content

Reticulocyte Hb concentration determines the amount of iron available to the bone marrow for incorporation into new RBCs. This test is not commonly available. The sensitivity and specificity of this test are comparable to those of serum ferritin (61).

Bone marrow iron

In order to make a definitive diagnosis, bone marrow biopsy should be considered, when the diagnosis remains ambiguous even after the analysis of laboratory results. The 'gold standard' for diagnosis of IDA is the absence of stainable iron.

Serum ferritin and Hb estimations are the most common tests for diagnosing IDA performed in the studies from India (62-66). WHO/CDC working group analysis has demonstrated Hb, MCV, ferritin, transferrin receptors, and ZPP as the best indicator of iron status (67).

Trial of Iron therapy

In situations with low Hb or hematocrit, a presumptive diagnosis of IDA is supported by a response to iron therapy. If the patient is suspected to have a hemoglobinopathy, serum ferritin has to be checked to confirm iron deficiency before starting iron therapy to avoid iron overload. An increase in Hb at week two confirms ID. Detailed investigations should be done if the individual does not respond to iron supplementation at two weeks (68).
The merits, demerits and reference ranges of all above parameters are as indicated in Table 6.

Table 6. Summary of iron indicators for the diagnosis of iron deficiency among adolescents

Biomarker	Advantages	Limitations	Cut-offs
Hemoglobin (Hb)	Easy, economical; good screening tool for severe iron deficiency	Neither sensitive nor specific for iron status; better measure of function rather than status	Normal: 12 g/dL or > Mild anemia:11-11.9 g/dL Moderate anemia:8-10.9 g/dL Severe anemia:<8 g/dL (37)
Hematocrit (Hct)	Relatively easy to measure	No additional information above Hb	<36% (68)
Mean cell volume (MCV)	Low MCV characteristic of iron deficient erythropoiesis	Late finding, not representative of iron status	<84fL (<12 y) <86fL (12-14.9 y) <88fL (15-17.9 y) <90fL (>18 y) (68)
Red Cell Distribution Width (RDW)	Increased RDW characteristic of iron deficient erythropoiesis		<11.5% or >14.5% (67)
Mentzer index	Inexpensive		>13(69, 70)
Serum or plasma iron	Measure of circulating iron	Easily contaminated by iron from other sources; variation by time of day, post-prandial state; does not detect iron contained in Hb	50-150 µg/dL (71)
Serum ferritin (SF)	Sensitive indicator of iron deficiency; proportionate to liver stores of iron; responds well to iron interventions	Increases with the acute phase response (not specific in the presence of inflammation)	<15 µg/L(71)
Transferrin saturation (Tfs)	Marker of circulating iron	Levels are depressed by inflammation	<15% (67)
Soluble transferrin receptor (sTfR)	Less sensitive to inflammation than SF Useful in populations with high levels of background infection	Not very sensitive; levels change only late in ID Not as specific as other measures; other conditions may cause restriction of iron to RBCs	≥10 mg/L (72)
Total iron binding capacity	More stable than other measures; measures iron-binding sites on	Changes only with depletion of iron stores	Normal: 256-350 µg/dL IDA: 380-442 µg/dL (73)

(TIBC)	transferrin		
Zinc protoporphyrin/ hemoglobin ratio (ZPP/Hb)	Sensitive indicator of severe iron deficiency, but not of moderate iron deficiency; can be measured with very little blood volume	Not specific as levels can be increased due to lead poisoning, inflammation, and other situations; cut-off levels not well established for infant populations	>80 µmol/mol (67)
Reticulocyte hemoglobin	Measure of iron availability to cells; ot affected by inflammation	Assay not yet widely available	≤25 pg (74, 75)

Management

Management of ID needs concerted efforts at two levels, one at the individual patient and the other at community level. Prevention strategies developed by WHO comprise food-based approach, iron supplementation and improvement in health services and sanitation. Other strategies, e.g. control of hookworm, malaria and parasitic infections are required to prevent IDA in Indian women (76).

Food based approach

The daily diet is the only source of iron supply and such dependence implies that bioavailability and absorption of this mineral determine whether or not their physiological requirement is satisfied. Nonheme iron (present in plant-based foods) absorption is inhibited by phytic acid (6-phosphoinositol) which is found in whole grains, lentils, and nuts. In addition, polyphenols, such as tannic and chlorogenic acids, found in coffee, tea, red wines, and a variety of vegetables, cereals and spices also inhibit iron absorption. They are capable of forming complexes with iron at physiological pH of 7.4 and alter the equilibrium concentration of free iron and thus influence bioavailability. Thus, while the daily physiological requirement of iron to cover basal loss, blood volume expansion, blood loss, muscle mass and to maintain body stores does not exceed 1.35 mg/day, the recommended dietary allowance (RDA) for adolescent girls is 27 mg/day (10-15 years of age) or 26 mg/day (16-17 years of age) for iron (77) reflecting relatively low bioavailability from the diet of 5%. This decreased bioavailability is a major etiological factor for iron deficiency in the adolescent population and enhancing bioavailability is considered to be the best approach for alleviating iron deficiency (78). Iron absorption inhibitors in diet such tannins should be discouraged, especially concurrent intake of tea with meals (79). Promoting the use of iron absorption enhancers like ascorbic acid is an effective way of increasing bioavailability of iron and the resultant improvement in Hb level (80-83). The dietary modification involves consciously increasing the consumption of iron rich and vitamin C rich foods (Guava, lemon etc) and following practices of simultaneous intake of minimally processed vegetables and fruits that increase the absorption of iron (84). Bioavailability studies in humans have shown that inclusion of about 100 g papaya or guava with major meals have the maximum iron enhancing property (85, 86). Changing dietary behaviors of adolescent girls have been shown to reduce the prevalence of anemia (87). Table 7 shows the iron content of some common Indian diet components to guide dietary diversification.

Table 7: *Iron rich food, (mg per 100g)* (88)

1. **Cereal grains and products**
   Whole Wheat flour atta (4.9), Ragi (3.9), Jowar (4.1), Samai (9.3)
2. **Pulses and legumes**
   Bengal gram roasted (9.5), Bengal gram dhal (5.3), Cow pea (8.6), Green gramwhole (4.4), Horse gram whole (6.77), Lentil (7.58), Dry peas (7.05), Soya bean (10.4)
3. **Leafy vegetables**
   Amaranth Polygonoides (Ramdana or Rajgeera)((27.3), Amaranth tristis (38.5), Beet greens (16.2), Bengal gram leaves (23.8), Cauliflower greens (40.0), Mustard leaves (16.3), Radish leaves (18.0)
4. **Roots and Tubers**
   Beet root (1.19), Carrot (1.03), Mango ginger (2.6), Onion small (1.2), Potato (0.48), Radish table (1.0)
5. **Other vegetables**
   Beans (2.6), Cowpea pods (2.5), Onion stalks (7.43)
6. **Nuts and oil seeds**
   Almond (5.09), Cashewnuts (5.81), Coconut dry (7.8), Garden cress seeds (100), Gingelly seeds (9.3), Groundnut (2.5), Niger seeds (56.7)
7. **Fruits**
   Ambada (3.9), Apricot dry (4.6), Currants, black (8.5), Dates dried (7.3), Watermelon (7.9), Peaches (2.4), Pineapple (2.42), Seethaphal (4.31)
8. **Meat and poultry**
   Beef meal (18.8), Egg, hen (2.1), Liver, sheep (6.3), Mutton, muscle (2.5)
9. **Milk and milk products**
   Cheese (2.1), khoa (5.8)

Food fortification is the concept of bringing a commonly consumed vehicle and a nutrient together which is an effective method for reducing IDA (99, 100). In India foods such as wheat, rice, and salt have been fortified with iron and tested in several RCTs. Double fortified salt (DFS) has been developed and tested efficacy by the National Institute of Nutrition (NIN), Hyderabad to address the dual problem of iodine and iron deficiency (89-92). Other, formulations have also been developed, adding value to salt fortification (103, 104,). Currently, DFS has been mandated in Government sponsored food and nutrition programmes like Mid-Day Meal (MDM) and Integrated Child Development Services (ICDS) in 2011(93). In a randomized controlled study, school children were assigned to either a wheat-based lunch fortified with sodium iron ethylene diamine tetra acetic acid (NaFeEDTA) or unfortified meal. The prevalence of IDA in the treatment group significantly decreased (62 to 21% compared to18 to 9% in control) after 7 months of treatment; there was also a significant rise in body iron store (mmol/kg

of body weight) with the fortified meal compared to control (94). There are two RCT with iron-fortified rice conducted among MDM beneficiaries in Hyderabad and Bangalore. Both these studies clearly demonstrated improvement in iron stores and reduction in iron deficiency anemia (95, 96). In another RCT, adolescent girls in rural Bangladesh were allocated to either multiple micronutrient fortified beverages or non-fortified beverages for 6 days/week over 12 months. Fortified beverages increased the Hb and serum ferritin at 6 months ($p < 0.01$). Adolescent girls in the non-fortified beverage group were more likely to suffer from anemia and ID (OR 2.04 and 5.38, respectively; $p < 0.01$). The fortified beverage increased weight, mid-upper arm circumference, and BMI over 6 months ($p < 0.01$). Moreover, continued treatment for additional 6 months did not improve the Hb concentration, but the serum ferritin level persistently increased ($p = 0.01$) (97). Supplementation with fortified biscuits enriched with iron amongst adolescent girls increased the iron status (98, 99). A systemic review of RCTs on food fortification or biofortification with iron, which included 60 trials, demonstrated increase in Hb (0.42 g/dL, 95% CI 0.28-0.56, $p < 0.001$), serum ferritin (1.36 g/L, 95% CI 1.23-1.52, $p < 0.001$), a reduction in the risk of anemia (RR 0.59, 95% CI 0.48-0.71, $p < 0.001$) and ID (RR 0.48, 95% CI 0.38-0.62, $p < 0.001$) (100). Another systematic review of food fortification studies in India, including 25 RCTs, has shown improvement in biological markers, particularly iron and iodine (101). A systematic review and meta-analysis of studies on multiple-micronutrient-fortified non-dairy beverage interventions in anemia and ID in school-aged children in low-middle income countries, demonstrated improvements in Hb (0.27 g/dL, 95% CI 1.19-4.33, $p = 0.004$; 8 studies) and serum ferritin (15.42 pmol/L, 95% CI 5.73-25.12; $p = 0.007$; 8 studies) and reduced risk of anemia (RR 0.58, 95% CI 0.29-0.88, $p = 0.005$; 6 studies), ID (RR 0.34, 95% CI 0.21-0.55, $p = 0.002$; 7 studies), and IDA (RR 0.17, CI 0.06-0.53, $p = 0.02$; 3 studies) (102).

Iron supplementation

The Rationale for Supplementation

The RDA of iron for adolescents in India is relatively high, which is unlikely to be met by the diet alone, because of poor accessibility, and availability of diversified food in the presence of varied socio-economic situation. The recommended dietary allowance for adolescents is 27 mg/day (10-15 years of age) or 26 mg/day (16-17 years of age) for iron (77). The average iron intake by adolescent girls is 8 mg/day that shows 18-19 mg deficit in dietary intake to

accomplish physiological needs. Hence, a daily consumption of ~25 mg elemental iron and folic acid (IFA) supplements is essential to suffice optimal intake of iron and prevent IDA. Iron supplementation is the most commonly used strategy in developing countries for prevention of IDA. The supplementation to prevent anemia targets at improving the ID and it may be community-based initiative while therapeutic supplementation aims at treating established IDA which is a part of the healthcare delivery system (68).

Oral iron

Intermittent versus daily iron

Controversy exists over intermittent versus daily supplementation of iron (103). "Mucosal block" hypothesis has been proposed for intermittent iron, wherein administration of iron every seven days allows time for the shedding of cells loaded with iron from a previous dose, thereby increases iron absorption (104, 105). The approach is attractive because the side effects are thought to be less noticeable, and it may be both operationally easier to manage at the community level and more sustainable over extended time periods (106). A Cochrane systematic review evaluating intermittent (1, 2, or 3 times/week on nonconsecutive days) iron supplementation in menstruating nonpregnant women has demonstrated improvement in Hb by 0.46 g/dL and ferritin by 8.3 μg/L and reduction of anemia risk by 27% compared with no intervention. Importantly, the review revealed that the intermittent iron had a 26% higher risk for anemia when compared with daily iron (107). Another recent Cochrane systematic review demonstrated that daily iron supplementation effectively reduced the prevalence of anemia (RR 0.39, 95% CI 0.25-0.60) and iron deficiency (RR 0.62, 95% CI 0.50-0.76) raised hemoglobin (mean difference 0.53 g/dL, 95%CI 4.14-6.45) compared with placebo or control (108). In another Cochrane review comparing intermittent (1 to 3 times/week) to no iron supplementation for children aged <12 years found that intermittent iron supplementation reduces the risk for anemia by 49% and the risk for ID by 76% and improves Hb and ferritin concentrations by 0.52 g/dL and 14.2 μg/L, respectively. When both intermittent and daily iron supplementation were compared, daily iron reduced the risk for anemia by a further 23%, but Hb and ferritin concentrations were similar (109). This review found daily administration of iron is more appropriate than intermittent supplementation in children where IDA is known to be highly

prevalent as in India, and universal screening for anemia is unavailable. In these settings, most individuals, in fact, require treatment (rather than prophylaxis) for ID (110).

A WIFS program (supervised administration of 500mcg folic acid with 100mg elemental iron once a week for 52 weeks a year along with biannual deworming with Tab Albendazole 400 mg single dose), an initiative by WHO, for women and adolescents have been successfully implemented in several countries including Cambodia, Vietnam, Egypt and India, and in most settings it has been found to reduce anemia, particularly where the baseline prevalence was very high (>40%) (22). Weekly iron and folic acid supplementation have been shown to be cost-effective; in a recent WHO report, the annual cost which was Rs 119.62 per beneficiary early in 2001-2002,was found to have reduced remarkably to Rs 14.60 per beneficiary in 2006 (22). Sustained political will, ensuring regular supply of IFA tablets, using a "Fixed Day" approach, have been demonstrated to be a positive element for effective operationalization of the program and for increasing compliance (111-113). A number of weekly iron and folic acid supplementation (WIFS) programs and trials were launched in the late 1990's and early 2000 in controlled program situations in some developing countries from Asia, Africa and South America. In a subsequent meta-analysis, which included 9 studies from developing countries, under highly controlled conditions, weekly and daily approaches had a similar impact on anemia prevalence. WIFS was recommended only in situations where there is a strong assurance of supervision and high compliance, basing on the results of the study (114). The results of WIFS intervention studies, and the studies evaluating varied frequency of iron supplementation in adolescent girls in India are presented in Table 8 and Table 9, respectively.

Table 8. The outcomes of weekly iron and folic acid studies in India

Author	Population Study period	Outcomes	% patients with ADR
Soni D et al 2015(115)	N= 55; Study period- 5 wks. Fe-100mg, Folic acid-500µg, Albendazole 400mg. Acceptability and compliance	Compliance: 1st wk-82%, 2nd wk-58%, 3rd wk-31 %, 4th wk-11%, 5th wk-0.2%	5.4%
Dhikale PT et al 2015(116)	N= 235; Study period-4 wks. Fe-100, Folic acid- 0.5mg	Compliance 85%	24.6 %
Bansal et al 2015(117)	N= 446; Study period- 26 wks; Fe-100mg,folic acid 500µg	Anemia reduced by 35.9% (A) and 39.7% (B) (p>0.05). Hemoglobin rise: A-10.67±1.12 to 11.64±1.08 g/dL (p < 0.001) B-10.89±0.89 to11.65±1.03 g/dL (p < 0.001)	-
Bhanushali et al 2011(118)	N=104;Study period- 3 months Fe-60mg, Folic acid-0.5mg	Hb: Increment of 19.55 g/L Compliance: 95%	-
Vir et al 2008(113)	N= 150,700;Study period-6 months; (WIFS+ education+ deworming)	Anemia reduced from73.3% to 25.4% (more significant in 6 months) Compliance > 85% WIFS+ deworming every 6 months is reasonable	18.7%
WH0 2011 Bihar state(119)	N= around 1,100,088; WIFS + 400 mg; Albendazole+ education; 1 year	Anemia decreased from 93.1% to 84.4% (p < 0.001) (significant reduction of 9.3% Compliance: 85.2% - 92.2%	-
Kotecha PV et al 2009(120)	N= 2860;WIFS + education Study period- 17 months	Anemia reduced from 74.7 % to 53.2 % (p < 0.05) Compliance >90 %	-
Deshmukh et al 2008(121)	N=300;Study period- 2 months Fe-100mg, folic acid-0.5mg	Anemia: Reduced from 65.3%-54.3% (p < 0.001) Hb: Increased from 110.7-113.7g/L (p < 0.05)	-
Ahmed et al 2001(122)	N=480;Study period- 12 weeks; Fe-120mg, Folic acid-3.5mg	Anemia reduced by 90% Hb increased from113g/L to 122g/L	-

ADR, adverse drug reactions; Hb, hemoglobin; WIFS, weekly iron and folic acid supplement

Table 9. Summary of comparative studies on iron supplementation in India

Author et al	Objective	Outcomes	Better outcome
Suhasini et al 2015(62)	Daily supplementation for 100days ferrous sulphate 65 mg and vitamin B12 15 µg (n=50)	Hb increased by 2.1 g% (p <0.001)	-
Jawarkar et al 2015(63)	Daily supplementation for 3 months (n=350) FE-152 mg; folic acid 750 µg	Anemia decreased from 55% to 25%. Hb increased from 10.57% to 11.78 g%	-
Lamba et al 2014(64)	Biweekly supplementation (n=300) Group A-IFA+Albendazole Group B-IFA	Anemia: A-80.7% to 35.5%; B-73.5% to 58.8% Hb increased by : A-2.5 g/dL; B-2.3 g/dL	-
Gupta et al 2014(65)	Weekly, bi–weekly, and daily regimen IDA (n=331) 335 mg ferrous sulfate-Fe-100mg, 500 µg of folic acid for 3 months	Hb increased by : Bi-weekly:3.1 g/dL); once weekly (2.4 g/dL) and daily groups (2.3 g/dL (P = 0.64) Side effects: Daily group-55%; Biweekly Group-25%; Weekly group-18% (p <0.001)	Biweekly
Joshi et al 2013(66)	Daily vs weekly supplementation, side effects and compliance for 3months (n=120) Fe fumarate-300mg, Folic acid-1.5mg	Anemia reduced by: Daily-25%; Weekly-31.67% Hb Increased by: Daily-1.04 g/dL; Weekly-1.0 g/dL (p < 0.001) Compliance: Daily-6.1%; Weekly-1.3% (p = 0.0012) Side effects: Daily-13.35%; Weekly-8.3%	Weekly
Chellappa et al 2013(123)	Daily supplementation (n=109) For cognition Fe-60 mg, Zinc-30 mg combined for a period of 4 months	Ferritin: Improvement in ferritin concentrations (p < 0.01) Side effects: 83%-86%	-
Sharma NK et al 2013(124)	Daily (A) vs WIFS (B) vs WIFS + education (C)	Increase in Hb was, A=10.1±0.13 to 12.32±0.12 g/dL (p < 0.0001), B= 10.28±0.15 to 12.39±0.13 g/dL (p < 0.0001), C= 9.94±0.13 to 12.75±0.15 g/dL (p < 0.0001) A= 32%; B= 12%; C= 16%	-

Chakma et al 2012(125)	Daily supplementation and identify factors associated with high compliance. (n=274) 100mg of elemental Fe and 350mg of folic acid for 100days	Anemia: Reduced from 94% to 69% Compliance: 88.8%	-
Sen et al 2012(126)	Daily vs. intermittent (once and twice weekly) iron folic acid supplementation. (n=254) 100 mg Fe+0.5mg folic acid for year	Hb Increased Twice weekly-1.6 g/dL; Daily-1.9 g/dL; Weekly-1 g/dL ($p < 0.01$) Compliance: 72%	Twice weekly
Kakkar et al 2011(127)	Bi weekly supplementation (n=317) Fe-100mg, Folic acid-500mcg for 3 months	Hb increased from 11.2-12.6 g%	-
Sen et al 2009(128)	Once weekly vs twice weekly vs daily (cognition) (n=161). (100 mg elemental iron + 0.5 mg folic acid) either for one year.	Hb increased by : Daily- 1.9 g/dL; Weekly- 1.6 g/dL ($p < 0.001$) Compliance: 72%	Twice weekly
Agarwal et al 2003(129)	Weekly vs daily Fe-100mg, Folic acid-500µg 4 months	Anemia decreased: Daily-48.5 to 37.2; Weekly-52.3-38.1 Hb increased from-Daily-11.7-12.2 g/dL; Weekly-11.7-12.1	Weekly
Trivedi et al 2007(130)	Once a week vs twice a week vs thrice a week (n=360)	Hb increased (g/dL): Once a week- 10.79-12.65 g/dL; Twice a week-10.69 -14.10; Thrice a week 10.73-14.63	Twice a week
Mehnaz et al 2006(131)	Daily supplementation for 100 days (n=177), Fe-200mg, Folic acid-0.5mg	Anemia: 72% to 36% Hb: 2.72g/dL ($p < 0.0.5$)	Daily
Shobha et al 2003(132)	Daily vs twice weekly for 12 weeks. (n=244), 60 mg of iron, 0.5 mg of folic acid	Hb Increased: Severe: 58.78% in daily and 52.64 in weekly Moderate: 33.44% in daily and 29.69 in weekly Mild: 23.22% in daily and 18.95% in weekly Side effects: Daily-57.84%; Weekly-94%	Twice weekly
Sharma et al 2000(133)	Once 'weekly' vs 'daily' for 3 months, including compliance	-	Once weekly

Hb, hemoglobin; IFA, iron folic acid; WIFS, weekly iron and folic acid supplement

Optimal dose for supplementation

In a Cochrane systematic review, the doses of elemental iron varied from 1 mg to approximately 300 mg, but there was no difference in the effect of iron on Hb according to the dose of iron administered (108). Moreover, there was a trend towards an increase in risk of GI adverse effects as the dose of elemental iron was increased: from 31 mg to 60 mg (RR 1.23, 95% CI 0.84-1.81), to 61mg to 100mg (RR 3.00, 95%CI 1.45-6.20), to more than 100 mg (RR 2.42, 95% CI 1.45-4.05) (108). Taking into account results of the Cochrane review (108) and the average intake of 8mg/day against RDA of ~26-27 mg by adolescent girls in India (77), a daily supplementation of 20-30 mg elemental iron may offer optimal dose for prevention of anemia with a low incidence of GI side effects. As shown by the Cochrane review, Hb levels increased more when daily supplementation was given for one to three months (Mean Difference 0.61 g/dL, 95% CI 4.70-7.58) compared to less than one month (MD 0.26 g/dL, 95% CI 0.28-4.9) or greater than three months (MD 0.38 g/dl, 95% CI 0.94-6.75) (108). A summary of randomized trial investigating the efficacy of less than 30 mg of elemental iron is presented in Table 10.

Table 10. Summary of efficacy of ≤ 30 mg oral iron in randomized trials

Author	**Number of patients; Mean age (y)**	**Study duration**	**Intervention**	**Outcomes**
Wang 2012 (134)	N=74; 21 to 45	6 months	Intervention: ferric pyrophosphate and ferrous fumarate (8 mg elemental iron) daily Control: placebo	Hb and SF of the study group were significantly higher (P < 0.01) than that in control group; Hb ≥12 g/dL : 15 (44.1%) in study group and 5 (14.3%) in control group (P < 0.01); ferritin ≥ 15 micro g/L: 11 (34.4%) study group and 4 (12.5%) control group respectively ($p < 0.05$)
Zavaleta 2000 (135)	N=198; 15	17 weeks	Intervention: ferrous sulphate 60 mg/d (20 mg elemental iron) administered Monday to Friday (i.e. 5 days per week) Control: placebo	Gains in Hb were 1.1 g/dL (daily), 0.68 g/dL (intermittent) and 0.16 g/dL (placebo); anemic subjects in the daily group (10.9%) was lower compared with the intermittent (17.3%) and the placebo (22.7%) groups (p <0.05.); Compliance-94%
Booth et al 2014 (136)	N=49; 20	7 weeks	Intervention: ferrous gluconate containing 18 mg of elemental iron + 0.5 mg of folate daily Control: 0.5 mg of folate daily	Hb: 13.5 to 13.5 g/dL; mean decline in SF concentration of 30% at mid-point (mean difference -9.2 µg/L; 95% CI: -14.4 to -4.4; p = 0.001); mean increase in TS (mean difference = 22.8 %; 12.6 to 33.0 95% CI; $p < 0.001$); mean decrease in sTfR concentration (mean difference = -0.27 mg/L; -0.41 to -0.14 mg/L 95% CI; $p < 0.001$)
Brutsaert 2003 (137)	N=20; 29	6 weeks	Intervention: elemental iron 10 mg as ferrous sulphate Control: placebo	SF increased from 12.41 ± 3.29 to 15.02 ± 2.22 µg/L; Hb: 14 ± 3 to 13.8 ± 2 g/dL; serum iron increased from 11.3 ± 2.0 to 22.7 ± 3.3 µmol/L
Cooter 1978 (138)	N=10; 18 to 24	4 months	Intervention: iron (18 mg) as ferrous fumarate daily Control: vitamin without iron daily	Iron supplementation was of no value in raising serum iron, TIBC, percent saturation, and Hb levels
Hinton 2000 (139)	N=42; 21	6 weeks	Intervention: 50 mg ferrous sulphate (8 mg elemental iron) capsules Control: placebo	Hb increased from 13.4 to 13.5 g/dL; SF increased from 10.38 to 14.52 µg/l; serum iron increased from 12.2 to 19.4 µmol/l; compliance: 91.4%

Hinton 2007 (140)	N=20; 28	6 weeks	Intervention: ferrous sulphate equivalent to 30 mg elemental iron Control: placebo	SF increased from 11.67 to 20.82 mg/L Hb decreased from 13.8 to 13.6 g/dL
Yadrick 1989 (141)	N=18; 25 to 40	10 weeks	Intervention: 25 mg iron + 25 mg zinc Control: 25 mg zinc alone	Significant increase in SF and no effect on Hb
Gunaratna 2015(142)	N=378; 21	6 months	Intervention: 30 mg of elemental iron + 0.4 mg of folate Control: 0.4 mg of folate	Hb: 10.9 g/dL in the folic acid arm, 11.1 g/dL in the folic acid and iron arm;11.4 g/dL in the folic acid, iron, and multivitamin arm; risk of hypochromic microcytic anemia in the folic acid and iron arm (17%) and the folic acid, iron, and multivitamin arm (19%).
Mujica-Coopman 2015 (143)	N=55; 32	3 months	Intervention: 30 mg of elemental iron daily as ferrous sulphate Control: placebo	Group 2 (30 mg of Fe plus 30 mg of Zn) had significant increase of Hb and total body iron than group 1 (Fe 30 mg) or placebo
Swain 2007 (144)	N=21; 40	12 weeks	Intervention: 5 mg iron as heme iron supplement Control: placebo	Increase in body iron with FeSO4 (127 ±29 mg) and electrolytic (115 ±37 mg), but not in the reduced (74 ± 32 mg) or heme (65 ± 26 mg) iron forms; ferritin: (9.9 ± 2.9µg/L) Electrolytic and FeSO4(6.4 ± 1.99µg/L)
Li 1994 (145)	N=80; 30	12 weeks	Intervention: elemental iron 20, 40 mg Control: placebo	Hb increased from 11.4 to 12.7 g/dL; SF increased from 9.7 to 30.0 µg/L
McClung 2009 (146)	N=171; 20	8 weeks	Intervention: 100 mg ferrous sulphate, found to have a mean elemental iron content of 15 mg Control: placebo	Hb levels increased from 12.3 to 13.0g/dL; ferritin levels decreased from 37.0 to 32.0 ng/mL; compliance 94%
Viteri 1999 (147)	N=81; 22	3 months	Intervention: iron (60 mg as ferrous sulphate; 20 mg elemental iron) + folate (250 mcg) Control: folate alone	Hb levels were 13.4 – 13.8; 13.6 to 13.9; 13.4 to 13.8 g/dL in Group A, B and C respectively; ferritin: 24.3 to 25.7, 5.5 to 31.2, 31.2 to 29.1 µg/L in group A,B and C respectively
DellaValle 2012 (148)	N=40 > 18 y	3 months	Intervention: 50 mg ferrous sulphate per capsule twice a day (i.e. 100 mg FeSO4, approximately 30 mg elemental iron daily) Control: placebo	Improvements in Fe stores (serum ferritin) in the Fe treatment group after controlling for baseline Fe stores (p = 0.07).

Hb, hemoglobin; SF, serum ferritin;; sTfR, serum transferrin receptors; TS, Transferrin Saturation; TIBC, total iron binding capacity

Iron preparations for supplementation

The commonly used iron preparations include ferrous sulfate, ferrous gluconate, ferrous fumarate, ferrous glycine sulphate, ferrous ammonium citrate, ferrous glycine, carbonyl iron, ferrous calcium citrate. All available iron preparations are effective with a variable timing of the response. Iron is active in ferrous form, hence, all the dietary iron need to be reduced to ferrous form to get absorbed by mucosal cells. The bioavailability of iron from ferrous salts is ~3-4 fold higher than ferric salts. This fact supports preference for bivalent ferrous salts such as ferrous sulfate, glutamate, gluconate, fumarate, succinate, and lactate over ferric salts. These preparations are relatively cheap and easily available. They have uniform bioavailability as well. Aminoacid conjugates of the ferrous or ferric ion form Iron amino-acid chelates. The main advantage of amino acid chelates is their absorption promoting action of chelates by binding to abortion inhibitors present in food (phytates, phosphatse, etc.) in small intestine. Theoretically, iron amino acid chelates offer the highest advantage. However, ferrous glycine sulphate has not been adequately studied and is costlier than ferrous sulphate. A stable complex of polymaltose with non-ionic iron, called iron polymaltose complex, is a novel salt. Although, it has been shown to produce lesser side effects, the efficacy of this salt has been a topic of debate recently (149). Carbonyl iron has a very small particle size, due to which it solubilizes in the presence of stomach acids. It has been well studied in adults, demonstrates satisfactory safety and efficacy (150). A multi-layered delayed release preparations of ferrous calcium citrate has a gastric resistant coating that allows its dissolution in the small intestine. Once released in intestine, calcium of this salts binds to phytates and phosphatase of food owing to higher affinity for them compared with iron. This spares ferrous for absorption and promotes iron absorption (151). Currently, there is insufficient evidence to arrive at any conclusion on better iron preparation. However, cost, availability, acceptance and compliance should be considered in prescribing iron and folic acid preparation.

Preventive supplementation

As a preventive measure, WHO recommend once a week, 60 mg of elemental iron with 2.8 mg of folic acid either throughout the year when feasible or for intermittently every 3 months (152). The Ministry of Health and Family Welfare (MoHFW) recommend weekly supervised IFA supplementation (100 mg elemental iron and 500 µg of folic acid) throughout the calendar year,

i.e., 52 weeks, each year with Albendazole (400 mg) tablets for biannual de-worming for helminth control. Good water and sanitary practices are encouraged like washing hands and wearing proper footwear by family members and beneficiaries (153). Details are shown in Table 11.

Therapeutic supplementation

The MoHFW recommends daily 60 mg elemental iron for the treatment of mild to moderate anemia (154). Following initial empirical treatment, if there is no response to 3 months of oral iron, further investigations are required to determine the cause of anemia (154). The MoHFW recommends, if Hb ≤4 g/dL, further investigations along with blood transfusion, as the first step for the treatment of severe anemia. Preferably, packed cells are administered at a rate of 10 ml/kg over 3-4 hours, if not available, whole blood at a rate of 20 ml/kg over 3-4 hours should be administered.

Possible side effects such as epigastric discomfort, nausea, diarrhea, or constipation may be seen with a daily dose of iron at 60 mg or more. Intake of iron with meals may help in reducing these symptoms to some extent. There is a darkening (blackish) of feces following oral iron therapy. All iron preparations inhibit the absorption of tetracyclines, sulphonamides, and trimethoprim. Thus, iron is preferably not combined with these agents (68).

Table 11. Summary of preventive iron supplementation

Guideline	**Preventive iron**
WHO 2011(152)	Once a week, 60 mg of elemental iron with 2.8 mg of folic acid either throughout the year when feasible or for intermittently every 3 months
WHO 2016 (155)	Daily 30–60 mg elemental iron for 3 consecutive months in a year
MoHFW (154)	Weekly 100 mg elemental iron and 500 mcg folic acid throughout the calendar year, i.e., 52 weeks each year

Parenteral iron

Parenteral iron can be a safe option in patients who did not receive or respond to oral iron due to intolerance, poor adherence, or iron malabsorption, suffering from GI diseases and inflammatory bowel diseases (IBD). Studies on initial intravenous versus oral iron therapy in adolescents are lacking. Various parenteral iron preparations are iron dextran, iron sucrose, iron gluconate, ferumoxytol, ferric carboxy maltose. Majority of published literature describe experience with iron sucrose and gluconate.

Iron sucrose gets rapidly available for erythropoiesis in bone marrow as shown by emission tomography studies. The studies also show that 70-97% of the iron is up taken for erythropoiesis, with only a 4-6% elimination (156). Iron sucrose has been associated with lower rate of adverse allergic reactions and the reported incidence is 0.002%, which is lower than that of dextran and ferric gluconate. Fatal hypersensitivity reactions and death have not been associated with iron sucrose (157, 158) Taking into account the rapid onset of action and good tolerability, it has been approved in the treatment of IDA in many clinical settings such as pregnancy and postpartum anemia, IBD, malignancies and chronic hemodialysis (156).The frequency of therapy can be, depends on the pre-treatment hematological values, indication, response to therapy, target hemoglobin, treating physician opinion, and centre experience.

A meta-analysis found that intravenous ferric carboxymaltose improved mean Hb, serum ferritin, and transferrin saturation levels; the mean end-of-trial increase over oral iron was, for Hb 0.48 g/dL (95% CI 3.3-6.3), for ferritin 163 μg/L (153-173), and for transferrin saturation 5.3% (3.7-6.8%). Ferric carboxy maltose was significantly better than comparator in the achievement of target Hb increase (159). In a cross-sectional study conducted in oral iron intolerant patients, the average increase in hemoglobin levels was 3.29 g/dL for women and 4.58 g/dL for men; 84% of female and 94% of male patients responded (hemoglobin increased by at least 2 g/dL) to intravenous iron therapy. Correction of anemia was obtained in 47 of 69 female (68.1%) patients and in 12 of 17 male (70.6%) patients (156).

Deworming

Intestinal helminthiasis and Hb concentrations are known to have an inverse relationship (160), hence, it has been proposed to administer anthelmintic agents as an additional intervention for reducing anemia. A systematic review of randomized controlled trials evaluating the effect of

routine administration of anthelmintic drugs on Hb demonstrated a mean Hb increase of 1.71 g/dL(161). In another systematic review, studying the impact of deworming on anemia in nonpregnant population, albendazole increased mean Hb by 0.19 g/dL (95% CI 0.13-3.63) while mebendazole had no impact (162). Evidence from Indian study shows that biannual deworming with IFA had an additional 17.3% increase in Hb compared to IFA alone ($p < 0.001$) (163). Deworming is currently recommended in combination with iron and folate supplementation to prevent the moderate and severe anemia and is the most effective strategy in the developing countries. Drugs include single doses of albendazole 400 mg; mebendazole 500 mg; levamisole 2.5 mg/kg; pyrantel 10 mg/kg. There is evidence to demonstrate that mild anemia was reduced from 64.5% to 35.5% and overall Hb rise was up to 2.5 g/dL (164). Deworming has been part of the anemia control program in many of the iron supplementation studies in India and is recommended by MoHFW, GOI for anemia prevention and treatment strategy (154).

Abbreviations

ACD	Anemia in chronic disease
CBC	Complete blood count
DFS	Double fortified salt
DLHS	District level household survey
DMT-1	Divalent metal transporter-1
EFF	Encapsulated ferrous fumarate
EPP	Erythrocyte zinc protoporphyrin
FOGSI	Federation of Obstetrician and Gynecology Society of India
GCPR	Good clinical practice recommendations
GDP	Gross domestic product
GI	Gastrointestinal
Hb	Hemoglobin
IBD	Inflammatory bowel disease
ICDS	Integrated child development services
ICMR	Indian council medical research
ID	Iron deficiency
IDA	Iron deficiency anemia
IFA	Iron and folic acid
IFS	Indian fertility society
LR	Likelihood ratio
MCH	Mean corpuscular hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean corpuscular volume
MDM	Mid-day meal
MGFePP	Micronized ground ferric pyrophosphate
MoHFW	Ministry of Health and Family Welfare
NaFeEDTA	Sodium iron ethylene diamine tetra acetic acid
NFHS	National family health survey
NIN	National Institute of Nutrition
NNMB	National nutrition monitoring bureau
RCTs	Randomized clinical trials
RDA	Recommended dietary allowance
RDW	Red cell distribution width
sTfR	Soluble serum transferrin receptor
sTfR-F	Soluble transferrin receptor-log [ferritin]
TIBC	Total iron binding capacity
UPP	Usual practice point
WHO	World health organization

WIFS	Weekly iron and folic acid supplementation
ZPP	Zinc protoporphyrin

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