# Iron Deficiency Anemia in Growing Years and its Effect on Cognition: A Review

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**Abstract:** Iron deficiency anemia is a widespread nutritional problem. Children are particularly vulnerable due to poor maternal iron status and inadequate diet. Since iron plays a vital role in neurological development, its deficiency in early life can lead to altered cognition and motor development. Severe iron deficiency during infancy can affect the major processes such as myelination, development of neurotransmitter pathways, neural metabolism and neural plasticity. The present review intends to provide information on the various effects of iron deficiency during different stages of life cycle. Clinical trials conducted on both humans and animals have established that infants who suffer iron deficiency during the early years of life are known to be under risk for experiencing the long lasting effect of early iron deficiency in future years also. Follow-up studies conducted on infants showed that the anemic children continued to exhibit lower cognitive development compared to their non-anemic counterparts and also had difficulty in the development of motor control tasks. Hence, there is a need to identify and correct iron deficiency anemia during the early years of life to prevent possible future complications.

**Keywords:** Prevalence of iron deficiency, motor development, premature infants, neurocognitive effects, iron absorption, iron supplements.

## INTRODUCTION

Iron deficiency anemia continues to be one of the major concerns all over the world. In developing countries, iron deficiency is found to be very common among children. An estimated 1-2 billion people worldwide, among them primarily women and children are affected by iron deficiency anemia [1]. Despite a decline in prevalence among industrialized nations iron deficiency remains to be a common cause for occurrence of anemia in young children [2-5]. About 80% of the iron stores of the newborn term infants are accredited during the 3$^{rd}$ trimester of pregnancy. In pre-term infants a deficit in total body iron is known to increase with decrease in gestational age. This condition is further worsened during the phases of rapid post-natal growth, especially in those infants who do not get adequate blood replacement [6, 7]. In a life cycle there are two stages at which iron requirement most likely exceeds iron intake, first stage is between 6-18 months of postnatal life and the second stage is during adolescence, specifically for girls. This accretion is necessary for various neuronal processes like myelination, neurotransmitter production and energy metabolism. During fetal and early postnatal life nutrition and growth factors regulate brain development. During 24 and 42 weeks of gestation the developing brain is particularly vulnerable to nutritional insult because of several neurologic processes including synapse formation and myelination which is said to be rapid [8].

All nutrients are considered essential for neural cell growth and development. But some are shown to have greater impact during the late fetal and neonatal periods [9]. Regions such as the hippocampus, the visual and auditory cortices and striatum undergo rapid development during late fetal and early neonatal life. Processes such as myelination accelerate during late fetal and early neonatal life and are vulnerable to nutrient deficits that support them [10, 11]. Evidence from animal and human studies has suggested that such deficiencies are associated with adverse effects on child cognitive and motor development [7, 12, 13].

Infants belonging to poor, minority and immigrant group are said to be at increased risk for developing iron deficiency anemia, though the prevalence is considerably less among industrialized nations. Attempts for reducing iron deficiency anemia exist because of its potential long term negative effects on individual functioning. Infants with severe iron deficiency exhibit poor functioning with respect to cognitive, affective and motor domain [14, 15]. Hence diagnosis of iron deficiency is very essential for initiating the therapy for combating its permanent effects.

## CAUSES

The iron status of newborn human infants can alter as a result of severe maternal iron deficiency anemia. Intrauterine growth retardation results due to maternal

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hypertension. In case of maternal diabetes mellitus, the demand for fetal iron increases to carry out the process of erythropoiesis and this results in lack of fetal iron accretion which is most commonly seen among premature infants [16-18]. Infants born to diabetic mothers were shown to have impaired auditory recognition memory processing at birth [19]. Premature infants with iron deficiency have a higher level of abnormal neurologic reflexes at 36 week post conception [20].

The hemoglobin concentrations of infants are normally higher at birth. At 2 months of age the hemoglobin concentration declines from 17g/dl to 11g/dl. This phenomenon is known as “early anemia of infancy”. A gradual shift occurs from an abundance of iron to the marginal iron reserves at about 4 months of age. Infants can become vulnerable to develop iron deficiency anemia during this window period. Hence this becomes a major focus of concern. The blood volume is known to expand rapidly during the period of 4-12 months and a large amount of iron is required to maintain a normal hemoglobin concentration of 12.5g/dl. During this period about 0.8mg of iron/day should be absorbed from the diet. Another diagnostic criteria to determine iron status is threshold values of ferritin. The cut-off points for normal hemoglobin and suggested thresholds for serum ferritin concentration for various age groups of children to be classified as iron deficient during epidemiological studies are given in Table **1**. Measurement of hemoglobin, serum ferritin, serum iron and transferrin (total iron binding capacity) enable iron status to be characterized in detail. Serum ferritin level is the most specific biochemical tests which can be correlated with body iron stores. Depleted iron stores result in low serum ferritin level, and are an indication of iron deficiency in the absence of infection [2].

Mild maternal iron deficiency and severe maternal anemia have strong influence on the iron status of the newborn infants. Apart from these reasons premature clamping of umbilical cord which is common in developing countries further increases the risk of developing iron deficiency anemia [23]. The absorption from dietary sources is minimal in the first two months of life and the stores get mobilized to meet the requirement of iron. Around 4-6 months of age supplementing dietary iron becomes very important since the body stores usually get depleted by this age. Both dietary and supplemental iron are important for low birth weight babies in whom the iron stores are generally low. Inadequate supply of iron in the diet is the commonest reason for the occurrence of iron deficiency anemia among infants. Iron is required for the synthesis of red blood cells (RBC). The growth and development is rapid at younger ages and to facilitate synthesis of RBC, diet should supply adequate iron. There are several other reasons where children may acquire anemia which includes; prolonged breast feeding without supplemental iron for premature and low birth weight infants, infants suffering with gastrointestinal diseases such as chronic infection, chronic diarrhea, celiac diseases or an intestinal parasite [24, 25].

According to a report published by the Government of India the incidence of anemia among male and female children was 69% and 69.9% respectively [26]. The prevalence rate for some of the states have been given in Figure **1**. Severe anemia was reported for 3.2% male children and 2.7% female children.

**Table 1: Cut-off Points for Various Diagnostic Parameters for Iron Deficiency for Different Age Groups Of Children [21, 22]**

| Age Group | Hemoglobin Concentration (g/dl) | Haematocrit Levels (µmol/l | Transferrin Saturation (%) | Free Erythrocyte Porphyrin (µg/dl) | Age Group | Serum Ferritin Concentration (µg/l) |
|---|---|---|---|---|---|---|
| 6- 59 months | 11.0 | 6.83 | <12 | >80 | 4 months | < 20 |
| | | | | | 6 months | < 9 |
| 5-11 years | 11.5 | 7.13 | <14 | >70 | 9 months | < 5 |
| | | | | | years | < 10-12 |
| 12-14 years | 12.0 | 7.45 | <16 | >70 | >5 years | < 15 |
| | | | | | 6-15 years | < 12 |

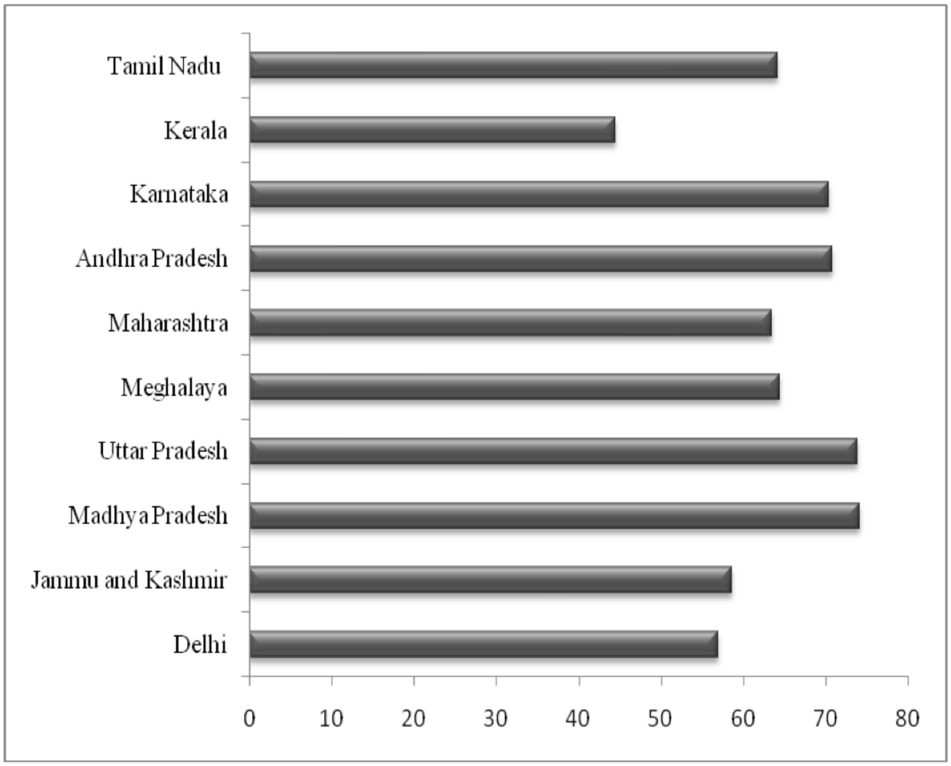


**Figure 1:** Prevalence of Anemia (%) among Children aged 6-59 Months in Different Indian States [27].

Percentage of children with severe anemia among severe anemic mothers was nearly seven times higher than that among non-anemic mothers. About 76.4% of children belonging to low income group were suffering from anemia, whereas 56.2% of children from high income group were anemic. The prevalence was found to be more than 70% in Bihar, Madhya Pradesh, Uttar Pradesh, Haryana, Chattisgarh, Andhra Pradesh, Karnataka and Jharkhand. In states of Goa, Manipur, Mizoram, and Kerala the prevalence was found to be less than 50%. For the remaining states, the anemia prevalence was in the range of 50-70% [27].

## ROLE OF IRON IN NEUROCOGNITIVE DEVELOPMENT

Iron deficiency leads to several medical sequel including growth retardation, impaired immune responses and poor temperature regulation [28-30]. Psychological and behavioral anomalies include; problems with emotional regulation and altered affective responding, impaired fine motor development and both general and specific cognitive delays [12, 31-35]. Study conducted by Beard on animal models identified that iron deficiency can have greatest impact on three major neurological mechanisms which include; myelination, development of neurotransmitter system, neural metabolism and also neural plasticity [31].

The mechanism by which iron deficiency anemia produces developmental and behavioral defects is uncertain. Several hypotheses have been postulated regarding this aspect. Early iron deficiency can have specific effects on the central nervous system. A brief period of iron deficiency in rat during the early brain growth spurt (10-28 days) results in lasting deficit in brain iron which is said to persist into adulthood despite correcting anemia. In an animal experimental model it was demonstrated that the neurotransmitter function was found to be altered in iron deficient rats. Noradrenaline activity gets impaired due to diminished levels of monoamine oxidase which is responsible for carrying out degradation processes. Also the activity of aldehyde oxidase which is involved in catalyzing serotonin degradation was found to be disturbed. These changes were known to induce drowsiness and altered attention and cognitive function in the iron deficient rat [36, 37]. The functional efficiency of dopamine Dd2 receptors were reported to be reduced in iron deficient rats. The behavioral activities mediated by dopamine are thought to be modified in the iron deficient rats [38]. The process of myelination was also found to be adversely affected. A drastic change in the fatty acid composition of myelin specific lipids such as cerebrosides was reported. Among moderately iron deficient rats the impairment in essential fatty acid metabolism was also observed [39, 40].

The iron containing cells in the human, mouse and rat brain are oligodendrocytes [31, 41]. These glial like cells within the central nervous system provide the myelin sheaths for long axons. Studies that have been conducted on rodents using pre and post natal iron deficiency paradigm have reported that the process of myelination was found to be disrupted by insufficient iron in the diet [42, 43]. Hypomyelination may also contribute to iron related delays in cognition. For example, in a study infants were subjected to Fogon test which is a good predictor of long-term cognitive abilities. The infants were tested for novelty preference and it was observed that infants who did not receive supplemental iron in preventive trial took more time for examining novel stimuli as compared to infants who received additional iron. This gives an indication that lack of iron affects processing speed [44]. The enzymes involved in carrying out specific brain functions are dependent on iron. These functions include myelination and synthesis of neurotransmitter. Iron also acts as a precursor to epinephrine and norepinephrine. The accretion of iron by human fetus begins during pregnancy which is said to increase in 3$^{rd}$ trimester. Preterm infants are vulnerable to develop deficiency because they have only 40-70% of total body iron as compared to term infants [6].

Evidence from long-term follow up studies have shown that the cognitive performance of children will show resistance to improvement when iron is supplemented for those who had suffered iron deficiency anemia at an early age. In a follow-up study conducted by Lozoff, *et al*. a group of Costa Rican children were examined [45]. The children were assessed by measuring intelligent quotient, verbal and qualitative learning, memory and attention. The assessment showed that children who formerly had iron deficiency anemia and who were treated for 3 months with iron, performed less well when they were reexamined at 5 and 11-14 years of age than that of control subjects (Table **2**). A longitudinal study has indicated that children who had suffered from chronic severe iron deficiency in the first year of life experienced long-term challenges with respect to cognitive, affective and motor development. For example, children scored lower on learning achievement, measures of persistence, self- control and attention when they were tested at 7 years of age among infants who had severe iron deficiency anemia during infancy in comparison with children of good iron status [46].

## EFFECT OF IRON DEFICIENCY DURING DIFFERENT STAGES OF LIFE

### Neonates

Relatively few studies have been conducted on the relationship of maternal iron status and subsequent neuro-development of the infants. A study was conducted by French scientists involving pregnant women, who were in the 2$^{nd}$ trimester of their gestation. The subjects were randomized and they were made to receive either 100mg of elemental iron throughout the remainder of their pregnancies or a placebo. As expected, iron treatment reduced iron deficiency markedly, most importantly three months after delivery. The serum ferritin concentrations were significantly higher in infants of women who received iron supplementation. The neuro-development was significantly better than the infants of mothers who were placebo treated [51].

In a long-term study the relationship between maternal iron status and infants' neuro-development and functioning was tested. The association was evaluated by comparing the fetal iron status with test scores of mental and psychomotor development at 5 years of age. It was observed that children in the lowest quartile scored lower on tests of cognition. The language ability, fine-motor-skills and tractability was poor compared to the infants in the highest two quartiles. This study implicated that iron-deficient infants were nearly 5 fold more likely to score poor in

**Table 2: Role of Iron in Brain Development**

| Required for | Effect of Deficiency | Reference |
|---|---|---|
| Myelination | Disrupts myelin sheaths and affects central nervous system functioning. | [31, 41] |
| Neurotransmitter synthesis | Alters the concentration of glutamate which is a primary excitatory neurotransmitter in the central nervous system. | [47] |
| Neural metabolism | Reduces metabolic activity especially in hippocampus and cingulated cortex. | [31, 48, 49] |
| Neural plasticity | Disrupts neural plasticity and reduces synaptic connectivity. | [50] |

fine-motor-skills and three fold more likely to have poor tractability than children in the median quartile. This study established the fact that effects of maternal iron deficiency is not restricted to prematurity and less fetal growth, but it can also lead to abnormal neural functioning in later life [52].

### Infants

Bayley's scale has been used in clinical intervention studies to evaluate the infant mental and motor development. Study conducted by Lozoff, *et al*. noted that iron deficient infants are said to be fearful, wary, hesitant, unhappy, tense and exhibit less pleasure and delight [44]. These behaviors reflect the developmental outcomes as they seem to interfere with stimulation and learning from the physical and social environment [12]. Healthy full term infants were recruited in preventive intervention trials by Moffatt, *et al*. to demonstrate the relationship between poor neural development and iron status. This preventive trial was conducted on impoverished infants which demonstrated a lower motor scores among iron deficient infants between the age of 9 and 12 months as compared to those of iron treated infants [53].

The effect of iron intervention in infancy and childhood was evaluated by Palti, *et al.* through long term follow-up studies [54]. After an iron intervention at 9 months of age developmental assessments were conducted at 2, 3 and 5 years of age. Children who were formerly moderately anemic showed lower cognitive development score at both 3 and 5 years of age than compared to non-anemic children of the same age. In a long term follow-up study conducted by Cantwell, *et al*. on infants of 6-18 months who were treated with iron and examined at 6 and 7 years of age, the recorded observations indicated that the subjects who were formerly anemic exhibited difficulty in the development of motor control tasks [55].

A reevaluation study was conducted by Lozoff on Costa Rican children who were tested and treated for iron deficiency when they were infants [45]. This reevaluation was carried out at 5 and 12 years of age. Of the total 191 participants 87% were reevaluated in early adolescence. Children who had chronic severe iron deficiency were compared with those who had good iron status before and/or after iron therapy in infancy. Children who had been iron deficient during infancy scored lower in arithmetic, writing, reading, school progress and motor function and also it was also observed that they had experienced more anxiety, depression and social problems. This study provides strong evidence that iron deficiency during early life is associated with cognitive and behavioral development because cognitive tasks involve the hippocampal and prefrontal cortex-striatal neural systems.

Wachs, *et al*. determined the effects of iron deficiency on infant temperament in a sample of 148 Peruvian newborns. Infant temperament was measured by examining activity level, negative emotions, alertness and soothability through a video-recorded standardized examination procedures [56]. The results indicated that lower levels of neonatal hemoglobin and serum iron was found to be associated with lower levels of soothability, alertness and negative emotionality was higher. In a double-blind trial, 221 Bangladeshi infants were randomly subjected to one of five different supplementary conditions; such as iron, zinc, iron and zinc, a micronutrient mix or riboflavin to evaluate the effect of weekly supplementation on infant behavior using a Bayley's scale [57]. Weekly supplementation was started at 6 months of age and was continued until 12 months. During the course of the study it was found that iron or zinc supplementation both individual or in combined form exerted a positive effect on exploratory behavior of infants. In a study by Akman, *et al*., it was reported that there seemed to be a positive relationship between weekly iron supplementation and normal motor development [14]. In this single blind study three groups of infants were selected whose age ranged between 6-30 months. They were divided as control, non-anemic with iron deficiency and iron deficiency anemia. Supplementation was given for a period of three months. Reevaluation of infants indicated that the supplementation helped normal fine motor development.

### Preschool Children

There is a paucity of data on preschool children which reveals the relationship between iron deficiency to cognition and behavior. In an intervention study Soewando and co-workers observed a cluster of effects of iron deficiency anemia on attentional control processes which could be reversed with two months of iron therapy [58]. In another study on the relationship between severity of iron deficiency to language acquisition and motor skills among young children, it was reported that the iron supplementation significantly improved language development to the extent of 0.8 points on a 20 point scale and improved motor development only in children having baseline hemoglobin concentration <90g/l [59].

Studies by Pollitt, *et al*. reported that the tests of discrimination, learning and attention items conducted for iron-deficient children indicated that they needed more trials to achieve a certain level of threshold compared to non-anemic children [60, 61]. Iron therapy for 3-4 months resulted in significantly improved performance of these 3-6 year old children. A study of iron deficiency prevention in India utilized a sample of preschool children to compare their responses to novelty and social looking behavior between children with iron deficiency anemia and those without whose age ranged between 47-68 months [62]. Children with iron deficiency anemia exhibited lower levels of social looking towards their mother and also demonstrated a hesitant behavior. These children were found to move more quickly to mothers and they were slow in touching a novel toy which was given for the first time. They also failed to express positive behaviour through smiling.

In a study by Corapci, *et al*., it was found that 5-6 year old children who were iron deficient during infancy exhibited lower levels of physical activity, positive effect and poor verbalization during mother-child interaction as compared to their non-iron deficient counterparts [63]. It was also noticed that the mother child reciprocity and mother's responsiveness to their children were lower for those children who had iron deficiency in infancy.

### Adolescents

Several intervention trials have examined the effects of iron deficiency on neural functioning among school-age, pre-adolescents and adolescent boys and girls [64, 65]. A study was conducted by Seshadri and Gopaldas among Indian subjects, who were recruited by matching their baseline hematological status, income, maternal education, height and weight prior to giving iron or placebo treatment [66]. After two months the study group was examined and the investigators could see greater improvement in verbal and mathematical test results, only among iron treated groups than the placebo treated group. An intervention trial was conducted by Soemantri, *et al*., to determine whether there is any relationship between learning and problem solving ability and iron status [65]. The study reported that the iron treated group showed significant improvement. In another study Bruner selected only iron deficient non-anemic adolescents to determine the impact of iron therapy on cognitive processes [67]. During the study period a wide range of tests of attention, learning and memory were administered to the participants. After two months of iron therapy again the tests were repeated and it was reported that iron therapy did help improve the iron status and memory task.

As already mentioned, the follow-up study by Lozoff, *et al*., on children of 11-14 years of age on assessing the interrelationship between cognitive deficits and iron deficiency anemia during infancy indicated that 48 children who had previously suffered from chronic iron deficiency in infancy showed lower scores in both writing and arithmetic skills compared to the 114, non iron-deficient children [45].

### Animal Studies

Clardy, *et al*. conducted a study on rat pups born to iron-deficient dams. Mothers' milk was supplied to pups till weaning and then they were fed with iron deficient diets till the 21$^{st}$ postnatal day (P21). The animals were either sacrificed or continued on iron-deficient diets for 6 months. The results revealed that at P21 the genes related to iron transport and myelin synthesis were found to be affected. A substantial down regulation of the mRNA was found to have affected the normal development of oligodendrocytes. However, after 5 months when iron was repleted the genes were found to be normal, the iron levels in the myelin were also normal [43]. This indicates that iron is integral to the basic development of oligodendrocytes and of myelogenesis. Gamma-aminobutyric acid (GABA) one of the primary inhibitory neurotransmitter which plays an important role in brain development, has been shown to be altered due to iron deficiency [43, 68, 69].

Another experimental study was conducted on rat pups that had been iron-deficient throughout the gestation period. At the end of the study period the animals were sacrificed and were analyzed for neural metabolic activity through the measurement of cytochrome - C - oxidase, (cytox) which is an enzyme required for oxidative phosphorylation. The results indicated a reduced cytox activity but the reduction was found to be not homogenous throughout the brain [49]. These metabolic deficiencies were noted only in areas involved with memory. This finding correlated well with better understanding of cognitive deficits that results due to iron deficiency in infants and young children.

Dietary deficiency of micronutrients can also affect neural plasticity which is the ability of the mammalian brain to be shaped by its experience which gets disrupted. Disruption of neural infrastructure and synaptic connectivity are the two major disorders

**Table 3: Review of Studies Showing Long Lasting Effects of Iron Deficiency**

| Place of Study | Method | Results | Reference |
|---|---|---|---|
| Israel | The hemoglobin concentration of subjects determined at 9 months of age and assessed again at 2, 3 and 5 years. | Demonstration of a positive association between hemoglobin concentration at 9 months of age to IQ level at 5 years. | [71] |
| France | Ten month old children belonging to immigrant population selected and followed up to the age of 4 years. | Hemoglobin concentration at 2 years of age showed a positive association with overall development in mental, motor and social quotients. | [72] |
| Yugoslavia | Iron deficient infants followed from birth to 4 years and hemoglobin levels determined at 6, 12, 18 and 24 months and at 3 and 4 years. | Hemoglobin level at 6 months predicted IQ at 4 years, as did hemoglobin level at 36 months of age. | [73] |
| Costa-Rica | Infants having varied iron status selected and treated with a full course of iron and tested after 5 years of age. | Lower test scores on IQ, perceptual speed, visual motor integration and fine motor performance seen in the group with moderate iron deficiency anemia. | [74] |
| Nepal | Evaluation of attainment of motor milestones in relation to iron deficiency. | Developmental delays in walking seen in anemic children as compared to normal children. | [75] |
| Zanzibar | Validity of iron deficiency levels on walking and crawling of infants was tested. | Iron status was shown to be a strong predictor of walking but not crawling. | [76] |
| United states | Investigation on the relationship between cord ferritin levels and psychomotor development of 5 year old children who were anemic as infants. | Children with lower ferritin score as neonates had poorer fine motor skills at the age of 5 years. | [52] |

observed in severe iron deficiency. Synaptic proliferation mainly occurs during infancy and iron deficiency can impair this proliferation and affect brain growth and development [50]. An examination of the micro structure of the brains of 15 day old rat pups which had been iron deficient both during pre- and post-natal life showed that the dendrites in the hippocampi were found to be truncated (Table **3**). This mainly results due to abnormal synaptic formation/function. Abnormalities in myelin formation and neurotransmitter binding and transport was also found to be affected [70].

## APPROACHES FOR THE PREVENTION OF IRON DEFICIENCY ANEMIA WITH REFERENCE TO INDIAN CHILDREN

One of the major goals of 12$^{th}$ five year plan of Government of India was to reduce anemia among women and girls by 50%. Under this initiative iron and folic acid supplements to children, adolescents, pregnant and lactating women are provided. For children 0-5 years 20mg elemental iron and 100µg folic acid in liquid form are supplemented along with deworming for 100 days. Children aged between 6-10 years, are provided with 30mg elemental iron and 250µg folic acid for 100 days. A weekly dose of 100mg elemental iron and 500µg folic acid along with biannual deworming is done for adolescent girls aged 10-19 years. The Ministry of Health and Family Welfare has recently introduced an 'iron +' initiative. This program brings together all the existing nutrition programs. Under this scheme bi-weekly iron supplement for preschool children aged from 6 months up to 5 years of age are given. Weekly supplementation is also extended to government and government aided schools for children studying in 1-5$^{th}$ grade. For adolescent girls, pregnant women and women of reproductive age supplementation is provided on weekly basis.

### Other Approaches for Combating Iron Deficiency Anemia

The iron intake can be increased through increased intake of iron rich foods i.e. through food based approaches. This includes dietary diversification, food fortification and supplementation. These are considered as important and sustainable strategies for preventing iron deficiency anemia. It is not easy to change established food habits or ensure adequate access to iron rich foods due to the fact that Indian diets are predominantly cereal based and bioavailability of iron from such diets is reported to be very low since, they contain higher amounts of phytates, oxalates and tannins in various components of the cereal grains. The bioavailability of iron from animal source is considered to be superior but its consumption is very low due to various social norms and poverty as animal foods are very expensive and outside the purchasing capacity of lower income families.

Creating awareness among the general population about the importance of exclusive breast feeding for the first 6 months of life, initiating appropriate and adequate complementary feeding with iron rich foods up to the age of 2 years should be followed. For increasing the bioavailability of iron it is important to reduce the intake of inhibitors of iron absorption and increase the intake of foods having enhancing properties. It is important to recommend the intake of vegetables rich in vitamin C, folate and other water soluble vitamins. Along with this the intake of germinated seeds, fermented cereals, heat-processed cereals and meat product consumption need to be increased. Consumption of tannin rich beverages along with meals as is often the norm in Asian countries should be discouraged. To bring about improvement in the level of adequacy and bioavailability of iron it is important to alter the meal pattern to facilitate enhancing factors and lower the inhibitory factors.

### Therapeutic Approaches

Therapeutic approaches are recommended for moderate and severe degree of iron deficiencies as a short term strategy to correct the deficiencies. The bi-weekly iron and folic acid supplementation regimen for various degrees of anemia are as given below [77, 78].

### *Children 6-60 Months and 5-10 Years Old*

- Mild anemia (10.0-10.9g/dl) – 3mg/kg/day for two months.
- Moderate anemia (7-9.9.0g/dl) - 3mg/kg/day for two months.

### *Adolescents*

- Mild anemia (11.0-11.9 g/dl) and moderate anemia (8.0-10.9 g/dl) – 60mg elemental iron daily for 3 months.

## CONCLUSION

Iron deficiency is still common in socioeconomically disadvantaged infants and toddlers. Iron deficiency anemia is usually associated with developmental delay and with poor growth. Iron and other micronutrients are essential for normal brain growth and development both before and after birth and any deficits result in compromised neuronal functions. Epidemiological studies indicate that cognitive functions of children can be compromised due to iron deficiency and some of these changes are irreversible. Effective preventive strategies have to be implemented to prevent this micronutrient deficiency among infants and young children. Iron deficiency can be treated through prompt dietary intake as well as through appropriate supplements. It is important to include iron rich ingredients in the preparation of complementary foods. The mothers of the children should be counseled regarding the importance of dietary diversification and including animal products in a diet. Judicious meal combinations with iron enhancers can increase iron absorption from foods. Fruits or fruit juices consumed along with meals or use of acidulants such as tamarind can increase iron absorption significantly from traditional diets. The ethnic practice of cooking in iron pots has also been shown to increase bioavailable iron and improve iron status. As an effective approach, the iron fortified foods can be made available at a reasonable cost to all the underprivileged populations.

## REFERENCES


[1] UNSCN. Progress in Nutrition. 6th Report on World Nutrition Situation. WHO, Geneva, 2011.

[2] ACC/SCN. Nutrition throughout the life cycle. 4th Report on World Nutrition Situation, Global and Regional Results, WHO, Geneva. 2000.

[3] Sherry B, Mei Z, Yip R. Continuation of the decline in prevalence of anemia in low income infants and children in 5 states. Pediatrics 2001; 107: 677-82. http://dx.doi.org/10.1542/peds.107.4.677

[4] Gulbis B, Jauniaux E, Decuyper J, Thiry P, Jurkovic D, Campbell S. Distribution of iron and iron binding proteins in first-trimester human pregnancies. Obstet Gynecol 1994; 84: 289-93.

[5] Ehrenkranz RA. Iron requirement of preterm infants. Nutrition 1994; 10: 77-8.

[6] Rao R, Georgieff MK. Early nutrition and brain development. In: Nelson C. A. Ed, The effects of early adversity on neurobehavioral development. Minnesota symposium on child psychology. Erlbaum Associates, Hillsdale NJ 2000; 31: 1-30.

[7] Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status; a longitudinal analysis of cognitive test scores to age 19 years. Arch Pediatr Adolesc Med 2006; 160: 1108-13. http://dx.doi.org/10.1001/archpedi.160.11.1108

[8] Enkson KM, Jones BC and Beard JL. Altered function of D1 and D2 dopamine receptors in brain of iron deficient rats. Physiol Pharmacol Behav 2001; 69: 409-18.

[9] Georgieff MK, Rao R. The role of nutrition in cognitive development. In; Nelson CA, Luciana M (Eds). Handbook of Developmental Cognitive Neuroscience. Cambridge. MA; MIT Press 2001; 491-504.

[10] Thompson RA, Nelson CA. Developmental science and the media; Early brain development. Am Psychol 2001; 56: 5-15. http://dx.doi.org/10.1037/0003-066X.56.1.5

[11] Nelson CA, Bloom FE, Cameron JL, Amaral D, Dahl RE, Pine D. An integrative multidisciplinary approach to the study of brain-behavior relations in the context of typical and atypical development. Dev Psychopathol 2002; 14: 499-520. http://dx.doi.org/10.1017/S0954579402003061

[12] Granthan-Mcgregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001; 13: 649-68.

[13] Lozoff B, Georgieff MK. Iron deficiency and brain development. Semin Pediatr Neurol 2006; 13: 158-65. http://dx.doi.org/10.1016/j.spen.2006.08.004

[14] Akman M, Cebeci D, Okur V, Angin H, Abali O, Akman AC. The effects of iron deficiency on infants developmental test performance. Acta Paediatrica 2004; 93: 1391-6. http://dx.doi.org/10.1111/j.1651-2227.2004.tb02941.x

[15] Begovic HE, Sebanovic S. Effects of iron therapy on motor and mental development of infants and small children suffering from iron deficiency anemia. Bosnian Medicinski Archiv 2004; 58: 227-9.

[16] Georgieff MK, Landon MB, Mills MM. Abnormal iron distribution in infants of diabetic mothers; spectrum and maternal antecedents. J Pediatr 1990; 117: 455-61. http://dx.doi.org/10.1016/S0022-3476(05)81097-2

[17] Georgieff MK, Petry CE, Wobken JD, Oyer CE. Liver and brain iron deficiency in newborn infants with bilateral renal agenesis (Potter's syndrome). Pediatr Pathol 1996; 16: 509-19. http://dx.doi.org/10.3109/15513819609168687

[18] Rao R, Georgieff MK. Perinatal aspects of iron metabolism. Acta Pediatr Suppl 2002; 91: 124-9. http://dx.doi.org/10.1111/j.1651-2227.2002.tb02917.x

[19] Siddappa AM, Georgieff MK, Wewerka S, Worwa C, Nelson CA, De-Reigner RA. Iron deficiency alters auditory recognition memory in newborn infants of diabetic mothers. Pediatr Res 2004; 55: 1034-41. http://dx.doi.org/10.1203/01.pdr.0000127021.38207.62

[20] Armony-sivan R, Eidelman A, Lanir A, Sredni D, Yehuda S. Iron status and neurobehavioral development of premature infants. J Perinatal 2004; 24: 757-62. http://dx.doi.org/10.1038/sj.jp.7211178

[21] UNICEF/UNU/WHO. Iron deficiency anemia- assessment, prevention and control. A guide for programme managers. Geneva, WHO. 2001; 33.

[22] WHO. Assessing the iron status of populations. II Edn., Geneva, Switzerland. WHO & CDC 2004.

[23] Gupta R, Ramji S. Effect of cord clamping on iron stores in infants born to anemic mothers: A randomized controlled trial. Indian Pediatr 2002; 39: 130-5.

[24] Stoltzfus RJ, Muslany L, Black RE. Iron deficiency anemia, comparative quantification of health risks; global and regional burden of disease attributable to selected major risk factors. Geneva; WHO. 2005; Vol I: 163-209.

[25] WHO. Indicators for assessing iron deficiency and strategies for its prevention (Draft based on a WHO/UNICEF/UNU consultation, 6-10th December 1993) Geneva 27, Switzerland. WHO/UNICEF/UNU. 1993.

[26] GOI. Children in India, 2012- A Statistical Appraisal. Ministry of Statistics and Program Implementation, Government of India. 2012.

[27] NFHS, 2007. National Family Health Survey (NFHS-3) 2005-06. International Institute for Population Sciences, Mumbai, India.

[28] Kapil U, Bhavna A. Adverse effects of poor micro nutrient status during childhood and adolescence. Nutr Rev 2002; 60: 84-90. http://dx.doi.org/10.1301/00296640260130803

[29] Yehuda S, Rabinovitz S, Mostofsky DI. Nutritional deficiencies in learning and cognition. J Pediatr Gastroenterol Nutr 2006; 43: 22-5. http://dx.doi.org/10.1097/01.mpg.0000255847.77034.a4

[30] Youdim MB, Yehuda S. The neurochemical basis of cognitive deficits induced by brain iron deficiency. Involvement of dopamine-opiate system. Cellu Mole Biol 2000; 46: 491-500.

[31] Beard JL. Recent evidence from human and animal studies regarding iron status and infant development. J Nutr 2007; 137: 524-30.

[32] Pollitt E. Developmental sequel from early nutrient deficiencies; conclusive and possibility judgements. J Nutr 2000; 130: 350-3.

[33] Black MM. Micro nutrient deficiency and cognitive functioning. J Nutr 2003; 133: 3927-31.

[34] Hubbs-Tait L, Natian JR, Krebs NF, Bellinger DC. Neurotoxicants, micronutrients and social environments. Individual and combined effects on children's development. Psychol Sci Public Inter 2005; 6: 57-121. http://dx.doi.org/10.1111/j.1529-1006.2005.00024.x

[35] Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006; 64: 34-43. http://dx.doi.org/10.1301/nr.2006.may.S34-S43

[36] Symes AL, Missala K, Sourkes TL. Iron and riboflavin dependent metabolism of a monoamine in the rat *in vivo.* Science 1971; 174: 153-5. http://dx.doi.org/10.1126/science.174.4005.153

[37] Mackler V, Person R, Miller LR, Inamdar AR, Finch CA. Iron deficiency in the rat: biochemical studies of brain metabolism. Pediatr Res 1978; 12: 217-20. http://dx.doi.org/10.1203/00006450-197803000-00011

[38] Yehuda S. Neurochemical basis of behavioural effects of brain iron deficiency in animals. In: Dobbing J, Ed. Brain behaviour and iron in the infant diet. Springer-Verlag, London. 1990; 63-81. http://dx.doi.org/10.1007/978-1-4471-1766-7_7

[39] Larkin EC, Jarrett BA, Rou GA. Reduction of relative levels of nervonic to lignoceric acid in the brain of rat pups due to iron deficiency. Nutr Res 1986; 6: 309-17. http://dx.doi.org/10.1016/S0271-5317(86)80134-8

[40] Cunnane SC, Mcadoo KR. Iron intake influences essential fatty acid and lipid composition of rat plasma and erythrocytes. J Nutr 1987; 117: 1514-9.

[41] Beard JL, Connor JR. Iron status and neural functioning. Ann Rev Nutr 2003; 23: 41-58. http://dx.doi.org/10.1146/annurev.nutr.23.020102.075739

[42] Kwik-Uribe CL, Gietzen D, German JB, Golub MS, Keen CL. Chronic marginal iron intakes during early development in mice results in persistent changes in dopamine metabolism and myelin composition. J Nutr 2000; 130: 2821-30.

[43] Clardy SL, Wang X, Zhao W, Liu W, Chase GA, Beard JL Acute and chronic effects of developmental iron deficiency on mRNA expression patterns in the brain. J Neural Trans 2006; 71: 173-96. http://dx.doi.org/10.1016/j.jns.2006.04.008

[44] Lozoff B, Deandraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. Pediatrics 2003; 112: 846-54.

[45] Lozoff B, Jimenez F, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics 2000; 105: e51. http://dx.doi.org/10.1542/peds.105.4.e51

[46] Shafir T, Angulo-Borroso R, Calatroni A, Jimenez E, Lozoff B. Effects of iron deficiency in infancy on patterns of motor development over time. Human Move Sci 2006; 25: 821-38. http://dx.doi.org/10.1016/j.humov.2006.06.006

[47] Ward KL, Tkac I, Jing Y, Felt B, Beard C, Connor J. Gestational and lactation iron deficiency alters the developing striatal metabolome and associated behaviors in young rats. J Nutr 2007; 137: 1043-9.

[48] Georgieff MK. Nutrition and the developing brain, nutrient properties and measurement. Am J Clin Nutr 2007; 85: 614-20.

[49] Ungria de M, Rao R, Wobken DJ, Luciana M, Nelson CA, Georgieff MK. Perinatal iron deficiency decreases cytochrome oxidase (cytox) activation in selected regions of neonatal rat brain. Pediat Res 2000; 48: 169-76. http://dx.doi.org/10.1203/00006450-200008000-00009

[50] Uauy R, Mena P, Peirana P. Mechanism for nutrient effects on brain development and cognition. In Nestle Nutrition Workshop series Clinical and Performance Program. Fernstorm JD, Uauy R, Arroyo P (Eds). Nutrition and Brain. S. Karger, Basel, Switzerland. 2001; Vol 5: 41-72.

[51] Preziosi P, Prual A, Galan P, Daouda H, Boureima H, Hercberg S. Effect of iron supplementation on the iron status of pregnant women; consequences for newborns. Am J Clin Nutr 1997; 66: 1178-82.

[52] Tamura T, Goldenberg RL, Hou J, Johnston KE, Cliver SP, Ramey SL. Cord serum ferritin concentration and mental and psychomotor development of children at 5 years of age. J Pediat 2002; 140: 165-70. http://dx.doi.org/10.1067/mpd.2002.120688

[53] Moffatt MEK, Longstaffe S, Besant J, Dureski C. Prevention of iron deficiency and psychomotor decline in high risk infants through the use of iron fortified infant formula; a randomized clinical trial. Pediatrics 1994; 125: 527-34. http://dx.doi.org/10.1016/S0022-3476(94)70003-6

[54] Palti H, Pevsner B, Adler B. Does anemia in infancy affect achievement on developmental and intelligence tests. Hum Biol 1983; 55: 189-94.

[55] Cantwell RJ. The long term neurological sequelae of anemia in infancy. Pediatr Res 1974; 342: 68.

[56] Wachs TD, Pollitt E, Cueto S, Jacoby E, Creed-Kanashiro H. Relation of neonatal iron status to individual variability in neonatal temperament. Develop Psychobiol 2005; 46: 141-53. http://dx.doi.org/10.1002/dev.20049

[57] Black MM, Baqui AH, Zaman K, Persson LA, Arifeen AE, Le K. Iron and zinc supplementation promote motor development and exploratory behavior among Bangladeshi infants. Am J Clin Nutr 2004; 80: 903-10.

[58] Soewando S, Husaini MA, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children; Bandung; Indonesia. Am J Clin Nutr 1989; 50: 667-74.

[59] Stoltzfus RJ, Kvalsvig JD, Chwaya HM, Mantresor A, Albonico M. Effects of iron supplements and anthelminthic treatment on motor and language development of preschool children in Zanzibar. Double blind placebo controlled study. Br Med J 2002; 323: 1389-93. http://dx.doi.org/10.1136/bmj.323.7326.1389

[60] Pollitt E, Leibel RL, Grenfield D. Iron deficiency and cognitive test performance in preschool children. Nutr Behav 1983; 1: 137-45.

[61] Pollitt E, Saco-Pollitt C, Leibel RL, Viteri FE. Iron deficiency and behavioral development in infants and preschool children. Am J Clin Nutr 1986: 43: 555-65.

[62] Lozoff B, Corapci F, Burden MJ, Kaciroti N, Angulo-Barroso R, Sazawal S. Preschool-aged children with iron deficiency anemia show altered affect on behavior. J Nutr 2007; 137: 683-9.

[63] Corapci F, Radan AE, Lozoff B. Iron deficiency in infancy and mother-child interactions at 5 years. J Dev Behav Pediatr 2006; 27: 371-8. http://dx.doi.org/10.1097/00004703-200610000-00001

[64] Kashyap P, Gopaldas T. Impact of hematinic supplement on cognitive function in under privileged school girls (8-15 years of age). Nutr Res 1987; 7: 1117-26. http://dx.doi.org/10.1016/S0271-5317(87)80037-4

[65] Soemantri AG, Pollitt E, Kim I. Iron deficiency anemia and educational achievement. Am J Clin Nutr 1985; 42: 1221-8.

[66] Seshadri S, Gopaldas T. Impact of iron supplement on cognitive functions in preschool and school aged children. The Indian experience. Am J Clin Nutr 1989; 50: 675-86.

[67] Bruner AB, Joffe A, Duggan AK, Caella JF, Brandt J. Randomized study of cognitive effects of iron supplement in non-anemic iron deficient adolescent girls. Lancet 1996; 348: 992-6. http://dx.doi.org/10.1016/S0140-6736(96)02341-0

[68] McCarthy MM, Auger AP, Perrot-Sinal TS. Getting excited about GABA and sex differences in the brain. Trends Neurosci 2002; 25: 307-12. http://dx.doi.org/10.1016/S0166-2236(02)02182-3

[69] Eseh R, Zimmerberg B. Age-dependent effects of gestational and lactation on iron deficiency on anxiety behavior in rats. Behav Brain Res 2005; 162: 214-21. http://dx.doi.org/10.1016/j.bbr.2005.06.019

[70] Jorgenson LA, Wobken JD, Georgieff MK. Perinatal iron deficiency alters apical dendritic growth in hippocampal CA1 pyramidal neurons. Develop Neurosci 2003; 25: 412-20. http://dx.doi.org/10.1159/000075667

[71] Palti H, Meijer A, Adler B. Learning achievement and behavior at school of anemic and non-anemic infants. Early Hum Dev 1985; 10: 217-33. http://dx.doi.org/10.1016/0378-3782(85)90052-0

[72] Dommergues JP, Archambeaud B, Ducot Y. Iron deficiency and psychomotor development scores. A longitudinal study between ages 10 months and 4 years. Arch Fr Pediatr 1989; 46: 487-90.

[73] Wasserman G, Graziano JH, Factor-Litvak P. Independent effects of lead exposure and iron deficiency are on developmental outcome at age 2 years. J Pediatr 1992; 121: 695-703. http://dx.doi.org/10.1016/S0022-3476(05)81895-5

[74] Lozoff B, Jiminez E, Wolf AW. Long term developmental outcome of infants with iron deficiency. New Eng J Med 1991; 325: 687-94. http://dx.doi.org/10.1056/NEJM199109053251004

[75] Siegel EH, Stoltzpus RJ, Kariger PK, Katz J, Khatry SK, Leclerg SC. Growth indices, anemia and diet independently predict motor milestone acquisition of infants in South Central Nepal. J Nutr 2005; 135: 2840-4.

[76] Kariger PK, Stoltzpus RJ, Olney D, Sazawal S, Black R, Tielsch JM. Iron deficiency and physical growth predict attainment of walking but not crawling in poorly nourished Zazibari infants. J Nutr 2005; 135: 814-9.

[77] GOI. Guidelines for control of iron deficiency anemia: National iron + initiative; Ministry of Health and Family Welfare; Government of India. 2013.

[78] UNICEF. Prevention and control of anemia; A South Asia priority. UNICEF, 2002.

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http://dx.doi.org/10.6000/1929-4247.2014.03.04.5