Rationale of Iron Dosage and Formulations in Under Three Children

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National Family Health Survey(NFHS)-2 data shows that 74 percent children age 6-35 months are anemic(1). In Delhi, 64% children aged 9-36 months in an urban slum ICDS project were found anemic, 44% being in moderate to severe category(2). Many studies from various centers of rural and urban India over the last decade have shown such high prevalence(3). Associations between hemoglobin (Hb) concentration and psychomotor performance have been demonstrated at all stages of life. An Expert Consultation concluded that anemia impairs the mental and motor development, and the behaviour of infants(4). There is also apprehension that developmental deficits that occur due to iron deficiency in infancy may be irreversible(5). Thus prevention of IDA in infants and growing children is an urgent need for improving the quality of life of our children.

Iron Balance 0- 6 moths

The first four months of term infant's life are characterized by a stage of iron abundance. Most newborns have a generous supply of transplacentally transmitted storage iron (6). At birth, iron stores of term infants is approximately 75 mg/kg(7). Due to hypoxic intrauterine environment, Hb value is high at birth(range 15-17 g/dl). This Hb represents substantial reserve of iron, since its concentration declines by 10 g/L/week over next 6-8 weeks, resulting in temporary augmentation of iron stores. Only later do iron stores begin a period of rapid decline as more active red cell production resumes keeping pace with a rapidly expanding blood volume. There is essentially no change in the total iron in the first 4 months of life though there is a near doubling of body weight. However, the distribution of iron changes. About half of the storage iron is mobilized for the production of Hb, myoglobin, and iron enzymes. Thus healthy term infants are unlikely to become iron-deficient before 6 months of age(8,9).

However, babies who are born preterm, have low birth weight(10) or born to anemic mothers(11,12) have poor iron stores at birth and could manifest with iron deficiency and anemia in the first three to six months of life. Feto-maternal and other perinatal hemorrhagic events, chronic blood loss and iatrogenic factors like frequent blood sampling could also lead to early development of anemia.

Iron Balance 6-12 months

After 4-6 months of age, iron stores at birth are no longer sufficient to meet the requirements arising due to increased growth and cumulative basal losses of iron.

Between 4 and 12 months the body iron requirement increases by 70% and the major amount has to come from the diet. Dietary issues contribute significantly to the evolution of IDA in infancy and early childhood(13). Approximately 20-40% of infants fed only non-iron-fortified formula or whole cow's milk and 15%-25% of breast-fed infants are at risk for iron deficiency by ages 9-12 months (14, 15). Early introduction of whole cow's milk adversely imbalances the iron status of the host, as it increases intestinal blood loss (16-18).The risk of IDA in infants fed breast milk without iron supplementation after four months of age has also been reported(19).

Iron Absorption from Human Milk

The iron content of human milk is highest in early transitional milk (0.97 mg/L) (20) but decreases steadily during lactation, reaching a level of approximately 0.3 mg/L by age 5 months (21). Iron intake from human milk averages 0.075 mg/kg at 1 month, 0.055 mg/kg at 2 months, and 0.048 mg/kg by 3 months of age (20,22). There is, however, a wide inter- and intraperson variability (23). The iron content of human milk does not seem to be affected significantly by the mother's iron status, maternal iron deficiency, or maternal iron therapy(24,25).

A typical estimate of iron absorption from human milk is approximately 50%; however, two studies using stable isotopes have questioned this high value and have reported absorption fractions of approximately 20%(26,27). Even taking a high estimate of iron absorption from human milk (50%) and assuming an iron intake from human milk of 0.075 mg/kg per day (20) less than 0.04 mg/kg per day is absorbed by term infants. This amount is much less than required for growth, and these infants therefore are largely dependent on stored iron until dietary iron intake increases.

Complementary feeding

In developing countries, not only complementary feeding often delayed beyond 6 months of age, the type of food usually given (cereals, legumes, milk, fruits, and vegetables) tend to be low in bioavailable iron. The inclusion of iron rich foods such as liver, meat or dry fish could help in this situation but these foods tend to be consumed rarely and in small amounts(28). This implies that some form of iron supplement is needed by most infants between 6 months and 2 years of age. After the age of 2 years, the prevalence of anemia tend to fall because iron requirement are lower and children start to consume a more varied diet(29).

Estimated Iron Requirements of Infants

Model 1

Iron requirements in infants may be estimated using a factorial approach that exploits the knowledge of the iron content of lean tissues and hemoglobin (30,31). *Table I* summarizes the average hemoglobin concentration during the first year of life and the average weight of breastfed infants, on the basis of which iron requirement of a hypothetical male infant is calculated(32,33). The iron content of lean tissues is approximately 7 mg/kg, so the tissue iron mass may be estimated by multiplying this number by an infant's weight. The circulating hemoglobin mass may be calculated from the weight, hemoglobin concentration, and blood volume (typically 75 mL/kg). In turn, this result may be converted to a hemoglobin iron mass because each gram of hemoglobin contains 3.47 mg of iron (30, 34). The iron content of newborn infants is approximately 75 mg/kg (30,35). By 1 month of age, only approximately 200 mg of iron is required to meet the needs for lean body mass and circulating hemoglobin (the sum of tissue iron mass and hemoglobin iron mass). It is not until after 4 months of age that the total body iron mass exceeds that present in newborn infants. These calculations ignore any iron losses, which are usually small but may be modified to account for storage of iron. Although crude, and ignoring the biologic variability of iron content at birth, these calculations are used widely (30,31,34) and suggest that newborn infants are unlikely to become iron deficient in early infancy but require iron supplementation after the age of 4 - 6 months.

TABLE I - *Iron requirements of hypothetical male infants estimated using a fractional method(32)*

Age (mo)	Hb (g/dL)	Weight (kg)	Tissue Iron (mg) *	Hb-Iron (mg) **	Total Body Iron (mg) §	Iron Requirement Since Birth	
						mg/d	mg/kg/d
0	14.5	3.49			262 +	--	--
1	14.1	4.58	32.1	168.1	200	-2.05	-0.51
2	11.4	5.50	38.5	163.2	202	-1.00	-0.22
3	11.2	6.28	44.0	183.1	227	-0.39	-0.08
4	11.5	6.94	48.6	207.7	256	-0.05	-0.01
5	11.5	7.48	52.4	223.9	276	0.10	0.02
6	11.5	7.93	55.5	237.3	293	0.17	0.03
9	11.8	8.89	62.2	273.0	335	0.27	0.04
12	11.9	9.62	67.3	297.9	365	0.29	0.04

Values of Hb and Wt. derived from Ref.33.

* Weight × 7 mg/kg; **Hemoglobin iron, assumes blood volume of 75 mL/kg, and that 1 g hemoglobin contains 3.47 mg iron; §Sum of tissue iron and hemoglobin iron.

+Assumes iron content at birth is 75 mg/kg.

Model 2

To meet the need for iron for growth and to replace normal losses, iron intake must supplement the approximately 75 mg of iron per kilogram of body weight that is present at birth. Iron losses from the body are small and relatively constant except during episodes of diarrhea or during the feeding of whole cow's milk, when iron losses may be increased.

About two thirds of iron losses in infancy occur when cells are extruded from the intestinal mucosa and the remainder when cells are shed from the skin and urinary tract. In the normal infant, these losses average approximately 20 µg per kilogram per day. An infant who weighs 3 kg at birth and 10 kg at one year of age will require approximately 270 to 280 mg of additional iron during the first year of life to maintain normal iron stores(*Table II*)(36).

TABLE II- Iron Requirement in Infancy

Characteristics	At Birth	At 1 Year
Weight (kg)	3	10
Hemoglobin (g/dl)	17.0	11.0
Blood volume (ml/kg)	90.0	75.0
Total Blood Volume (ml)	270.0	750.0
Total-Body Hemoglobin (g)	47.9	82.5
Iron in Hemoglobin (mg)	162.8	280.5
Iron in tissue (7mg//kg)	21.0	70.0
Stored iron (10 mg/kg)	30.0	100.0
Total-body iron	213.8	450.0
Total yearly iron losses(mg)*	-----	47
Exogenous iron requirement (mg)	-----	283
Daily iron requirement (mg)	-----	0.78

* At a rate of 20 mcg per kilogram of body weight per day.

The Committee on Nutrition of the American Academy of Pediatrics recommends that full term infants be provided with iron 1 mg/kg/d, starting at no later than four months of age and continuing until three years of age(37). For low birth weight infants, the requirement is 2 mg/kg/d, to a maximum of 15 mg/d, starting at no later than two months of age. Higher doses have been suggested for in the lowest birth weight categories(38). Infants with birth weights between 1000 and 1500 g should receive 3 mg/kg/d and infants with birth weight less than 1000 g should receive 4 mg/kg/d. For these infants iron supplementation at higher doses should continue throughout the first year of life.

Intervention trials

Intervention trials conducted in children below three are few. A recent one ((39) investigated the effect of iron supplements at the level of 1mg per kg body weight per day in a group of Swedish and Honduran infants, from the age of 4 mo to 9 mo. These infants were divided into three groups: i)that received iron supplements from 4 mo to 9 mo; ii)that received a placebo from 4 mo to 6 mo and then iron till 9 mo; iii) that received only placebo from 4 mo to 9 mo. The Honduran infants who received iron from 6 mo onwards showed a significant drop in the prevalence in anemia. In the Swedish infants of the corresponding group the prevalence of anemia to begin with was low and no further reduction occurred. However, the results of supplementation from 4 mo onwards produced a significant rise in Hb in both Honduran and the Swedish infants implying immature regulation of Hb synthesis at this age.

The recent meta analysis(40) of weekly vs. daily supplementation refers to four trials in young children, of which only one was in children 6 mo to 24 mo. The dose level of iron was 8 mg given along with zinc and retinol daily for 12 weeks. Reduction of anemia was very substantial, from the initial 50.9% to final 5.7%. These limited studies indicate that the dose level 1-2 mg/kg body weight that is equivalent to 10-20 mg iron can produce the desired results.

Iron Dose for Prevention of Anemia

From above discussion it is apparent that in a prophylactic program, between 1-2 mg iron/kg/d is adequate. Dose of 2 mg /kg/d could be considered in India as nearly one third babies born have low birth weight(1). However, in terms of implementing a community program for preventing anemia, use of iron dose in terms of body weight is impractical. A simple and suitable fixed dose strategy rather than an exact dose based on a body weight basis is more appropriate for a programmatic approach. Both International and National recommendations on such strategy are available, but because of their variance are needed to be examined.

Fixed Dose Strategy

International Nutritional Anemia Consultative Group (INACG) , based on a iron dose of 2 mg kg body weight for prevention of anemia, have recommended an uniform dose of 12.5 mg in 6-24 mo old children(41). This is based on assumption (42) of 5 percent iron absorption, which is a very conservative estimate of absorption. A 12.5-mg oral dose of iron would provide 0.625 mg of absorbed iron. The 12.5 mg dose is equivalent to 2.5 mg/kg body weight for a 6-month-old child with an average weight of 5 kg, 1.6 mg/kg body weight for a 12-month-old infant weighing 8 kg, and 1.2 mg/kg body weight for an 18-month-old infant weighing 12 kg. The total iron requirement remains at 0.7 mg per day for infants up to 18 months of age(43) and is not dependent on body weight; thus, the 12.5 mg dose would also meet almost 90 percent (assuming absorption 5% X 12.5= 0.625; 0.625/0.7 X 100= 89%) of the estimated total iron requirement of children 6 to 18 months old. Where iron absorption is higher because of low iron stores, the upper safe limit of intake would not be exceeded with this dose. If compliance were poor, and children were dosed the equivalent of every other day, between 35 and 45 percent of the iron requirement would be available from the iron supplement alone. This forms the basis of the INACG guidelines given below (*Table III*). More than 22 countries have now adopted iron supplementation of infants and preschool children as a public health policy on these lines(44).

TABLE III- INACG guidelines for iron supplementation to children (41)

Age group	Dosage	Birth-weight	Duration
6-24 months	12.5 mg iron +	Normal	6 to 24 mo of age
	50 µg folic acid/day	LBW(<2500 g)	2 to 24 mo of age
2-5 years	20-30 mg iron		2-3 weeks course several times a year

Notes:

For children 2-5 years, iron dosage is based on 2 mg iron/kg body weight/day.

National Nutrional Anemia Control Programme (NNACP) in India has recommended 20 mg of iron per day for children below the age of 5 years(45). Based on 5% iron absorption this dose would provide 1 mg of absorbed iron. National Consultation on Control of Nutritional Anemia has recommended this dose in liquid form to be targeted to 6-24 mo old children(46). If the average body weight of 6 mo-24mo old children is taken as 10 kg the prophylactic dose of 20 mg turns out to be 2 mg/kg/day. However, this dose could be equivalent to 4 mg/ kg in 6 mo old infant and thus the safety issue may need attention.

Therapeutic Dose of Iron

In an infant the blood volume is 75 ml/kg. Each gram of hemoglobin contains 3.4 mg of iron. In an average case of moderately severe anemia, Hb rises by about 1 g/dl/ week of iron therapy. Thus an infant weighing 10 kg with a blood volume of 750 ml, the total Hb generated in a week will be 7.5 g or nearly 1g / day. The amount of iron required to synthesize this amount of hemoglobin is 3.4 mg/ day or 0.34 mg/kg of elemental iron. The absorption of iron in mild to moderate iron deficiency anemia is higher – 13.5% (47). Assuming the bioavailability of iron to be around this figure the dose of elemental iron supplement required is approximately 2.5 mg/kg/d. Thus, 2-3 mg/kg of elemental iron once or twice daily between meals for four weeks should produce a rise of greater than 1 gm/dL in patients with iron deficiency anemia. Hematological response to oral intake can be achieved in 4-6 weeks with 3 mg elemental iron/kg/d; however, 1 mg/ kg/d will also have adequate response, but will take a little longer to correct Hb concentration,*i.e.* 3 months instead of 4-6 weeks(48) Iron absorption is increased if the iron is given with juice rather than milk (49). Iron should be continued in responders for two to three months to replace storage iron pools.

For infants with confirmed IDA 3 mg/kg of elemental iron, in divided doses, between meals with juice remains the standard therapy. Iron-fortified formulas and iron supplementation at these doses are infrequent causes of gastrointestinal symptoms (50). Larger doses rarely are necessary and may produce some degree of intolerance. In patients with severe IDA, a reticulocyte response may be seen in 72 hours. Treatment protocol based on fixed dose strategy is shown in *Table IV* (41).

TABLE IV: INACG guidelines for treatment of anemia(41).

Age Group	Dose	Duration
< 2 years	25 mg iron + 100-400 µg folic acid daily	3 months
2-12 years	60 mg iron + 400 µg folic acid daily	3 months
Adolescents	120 mg iron + 400 µg folic acid daily	3 months

Notes:
After completing 3 months of therapeutic supplementation, infants should continue preventive supplementation regimen.
Children with kwashiorkor or marasmus should be assumed to be severely anemic. However, oral iron supplementation should be delayed until the child regains appetite and starts gaining weight, usually after 14 days.

A daily protocol of iron supplementation is recommended for treatment and prevention in the infants. Many studies (51, 52) have evaluated whether the frequency of iron supplementation can be reduced from daily to twice or once per week in children but the evidence for such a protocol in infancy is still not sufficient.

Various Iron Salts

Iron liquid preparations contain iron salts/comlexes like ferrous sulphate, ferrous fumarate, ferrous gluconate, ferric ammonium citrate, colloidal iron and ferric hydroxide polymaltose complex (also called Iron Polymaltose Complex or IPC). Elemental iron content in these salt/complexes is variable (*Table IV*)(53). Generally the type of ferrous iron does not matter, but the type of iron does. The absorption of elemental iron depends on particle size. The particle size of electrolytic iron is favorable for absorption but it can be more expensive. EDTA has the advantage of greater stability than ferrous iron, good absorption and improves the absorption of non-heme in the diet. It only drawback is the higher cost. Amongst ferrous salts ferrous fumarate has a low ionization constant and high solubility in the entire pH range of the gastrointestinal tract. It does not precipitate proteins or have the astringency of ionizable forms of iron, and does not interfere with proteolytic or diastatic activities of the digestive system. Ferrous fumarate is the least toxic of three popular iron salts.

TABLE V- Elemental Iron Content of Various Iron Salts

Preparation	Approximate iron content(%)
Ferrous sulfate exsiccated	30
Ferrous sulfate (7H2O)	20
Ferrous sulfate, anhydrous	37
Ferrous fumarate	33
Ferrous gluconate	12
Ferrous carbonate	16
Ferrous glycine sulfate	23
Ferrous succinate	35
Iron choline citrate	12
Ferric chloride	44
Ferric sulfate	27
Ferric hydroxide	50
Ferric ammonium citrate	18
Ferric saccharate	10
Ferric pyrophosphate	25
Ferric orthophosphate	28
NaFeEDTA	14
Iron polymaltose complex	34
Colloidal iron	50
Hemoglobin	0.34

IPC is a novel iron preparation, which contains non-ionic ferric iron and polymaltose in a stable complex. Iron absorption from IPC is physiologically controlled and it is by an active process, where apotransferrin (a transferring molecule that does not contain iron) is found to take up the iron from IPC. It is then transferred to intestinal mucosa for further uptake by transferrin(54). The quantity of this carrier protein depends on the iron stores of the body. So iron absorption from IPC will be rapid in anemic condition and absorption will slow down or halt when the iron store reaches the optimum level. Hence there will be *no overloading* of iron with the use of IPC; unlike ferrous salts where iron absorption is passive and concentration gradient dependent(54). Bioavailablility generally is found similar particularly between ferrous sulphate, ferrous fumarate and IPC(55). Rise in Hb following nine weeks therapy with ferrous salts and IPC were also found similar(56).

Other advantages of Iron polymaltose complex is that it does not produce free radicals as opposed to conventional iron salts. Its non-ionic state helps in avoiding the gastro-intestinal irritation that is common with iron salts. IPC also do not stain the teeth and high elemental content of iron facilitates once a day dosing. Thus IPC may have a potential role in longer term supplementation programme (57).

A joint OMNI/USAID/UNICEF/USAID consultation has recommended that the most practical iron supplement for use in infants and young children is an aqueous solution of a soluble ferrous salt, such as ferrous sulphate or a ferric complex, such iron polymaltose. A single safe dose that is effective for all children under 2 years old that can be easily dispensed by nonliterate mother is required(58).Usually iron drops (or syrup) are given in two to three times daily dosing schedule. Recently, use of single daily dose of iron drops has been found to be equally efficacious as three times daily dose, (at the same total iron dose on treatment of anemia) without side effects(59).

Commercial Iron Liquid Preparations

Amongst commercially available iron liquid preparations, drops preparations are costlier in terms cost per 100 mg of elemental iron (*TableVI*). IPC seems to have cost advantage in this respect.

TABLE VI- Some iron liquid preparations available commercially

Brand	Pack(ml)	Type of iron	Elemental Iron (mg)	Shelf life (Yrs)	Cost* (100 mg E.Iron)
Drops					
Fevorit*	10	IPC	50/ml	2	4
Mumfer*	15	IPC	50/ml	2.5	4
Ferrochelate	15	Ferrric Amm.	20/ml	2	6
Tonoferron	15	Coll. Iron	25/ml	1	7
Syrup					
Fevorit *	150	IPC	50/5 ml	2	4
Haema*	150	IPC	50/ 5 ml	1	4

Vitcofol	200	Ferrous fum.	33/5 ml	1.5	2.5
Tonoferron	200	Coll. Iron	250/5 ml	1	1
Fesovit	100	Ferrous Sulp	33.4/5 ml	1.5	2

* Commercially available other IPC preparations (*e.g.* ferium, orofer, ferose have similar pricing and composition).
NB: Additives variable in preparations; IPC has long shelf life (2-5 yrs); Addition of B12 in formulations reduces shelf life to <2 yrs.

Other iron preparations

Recently, a supplement containing microencapsulated ferrous fumarate (plus ascorbic acid) has been developed which can be sprinkled on to any complementary food at the table by a caregiver. Iron being encapsulated does not change the color and taste of the food. The supplement is referred to as 'Supplefer Sprinkles' and is in sachet form. Studies in Africa have demonstrated efficacy, easy use and ready acceptance of such sprinkles(60). Exact dose of iron to be included in the sachet could range between 15-45 mg(61).

Dispensing of the iron supplement

Constraints of preventing and treating anemia in infants include poor compliance, the relative high cost of the iron solutions and droppers, and the lower stability of solutions, compared to tablets(58).Since the focus of the iron supplementation program in children is on infants, the obvious choice has to be a liquid formulation. This can be given in the form of drops or syrup. From the logistics point of view a concentrated solution of the iron solution dispensed in the form of drops would cut down on the cost of packaging and transport (in comparison to syrup). However, there is always the greater risk of accidental poisoning with such a preparation.

In view of this consultation held at UNICEF in 1996(58) recommended the following requirements for dispensing:i)Oral solution containing 25mg/ml of elemental iron in the form of ferrous sulfate or equivalent; ii)No deterioration in the composition, appearance and taste for 3 months after opening; iii) Shelf life of at least 3 years in unopened bottles;

iv) Acceptable palatability; v) For safety reasons the bottle should be designed such that 0.05 ml drops are directly dispensed into the child's mouth by simply inverting the bottle. The plastic orifice that produces the drops must be firmly attached to the bottle so that it is impossible for the child to accidentally consume the entire contents at one go.

National Consultation on Control of Nutritional Anemia has recommended(46) bottle of IFA syrup containing 100 ml (100 doses, each ml providing 20 mg of iron and 100 mcg of folic acid). If 12.5 mg/ day dose is adhered to it may be possible to have a smaller bottle containing 50 ml (each ml providing 25 mg of elemental iron as with colloidal iron); daily dose would be 0.5 ml equivalent to 10 drops. However, with IPC formulation having 50 mg of elemental iron/ml, daily dose would be 0.25 ml equivalent to 5 drops; an even smaller bottle containing 25 ml would be thus sufficient for 100 days.

With the INACG recommended schedule it would mean giving 5 drops of IPC (12.5 mg/ml) as preventive dose and 10 drops as therapeutic dose in 6-24 mo old children. Latter dose would also suffice as preventive dose in 2-5 year old children.

Under NNACP programme, IFA liquid formulation was discontinued in view of not being cost effective (Cost being Rs. 5.98 per beneficiary as compared to Re.0.49 for tab per beneficiary), and problems encountered in procurement and distribution of liquid preparations(62). Thus reintroduction of liquid preparations would need to address the problems encountered earlier.

Folic acid and Vitamin B12 requirements

Folic acid has long been included in iron supplements to prevent folic acid deficiency anemia. Addition of folic acid adds very little to the cost of iron formulations. There is, however, little evidence that folic acid deficiency is a public health problem in many developing countries. This may be explained by the considerable amount of folate in foods such as legumes, leafy vegetables and fruits. On the contrary, prevalence of B12 deficiency is likely to be high in developing countries, where animal products intake is low(63). In a recent study in young children only 5% anemic cases are shown to be folate deficient, whereas B12 deficiency was noted in 40% cases(64). Risk of Vitamin B12 deficient in infants as early as 3 months of age has been reported from other countries(65). Low birth weight and preterm babies could be at risk of folate deficiency due to rapid growth and would need supplementation of folic acid(66).Folic acid metabolism also requires an adequate Vitamin B12 status(67).Fortunately , only a severe deficit of folic and B12 results in anemia(63). Premature, low birth weight infants treated with iron, vitamin E, and folic acid showed an improvement in Hb concentrations when they were also given parenteral vitamin B12(68). For an infant normal daily requirement of folic acid is 25 mcg and of B12 is 0.2 mcg(69,70). However, dietary intake of cereal, pulses, fruits, leafy and vegetables are shown to be very low in children 9-36 months old children. The deficit in the case of green leafy vegetables is as high as 87% of recommended balanced diet(2). Thus, in a supplementation program, addition of 50 mcg of folic acid to iron formulation seems reasonable. Addition of 1 mcg of vitamin B12 per day could also be considered in view of high prevalence macrocytic anemia and B12 deficiency(2,64) . Other micronutrients particularly Vitamin A and riboflavin could play an important role in the causation of anemia (63).

Key Messages

- Preventive and therapeutic doses of iron would be 12.5 and 25 mg elemental iron per day in children 6 mo to 24 mo of age.

- For 2-5 years old children preventive dose of iron is 25 mg/d for 2-3 wks several times a year; therapeutic dose of iron folate would be 60 mg + 400 mcg per day for 3 mo.
- Preventive and therapeutic doses of folic acid would be 50 and 100 mcg per day in children 6 mo to 24 months of age.
- Role of other micronutrients need evaluation, as the data available is limited; however, addition of B12 may be considered.
- Use of IPC salt would be safe and advantageous needing a smaller packaging; dosing would also be simpler as preventive and therapeutic dose would be 5 and 10 drops respectively in 6-24 mo age groups.

REFERENCES

1. Report. National Family Health Survey-2 1998-1999. International Institute of Population Sciences, Mumbai, 2000.
2. Kapur D, Agarwal KN, Sharma S, Kela K, Kaur I. Iron status of children aged 9-36 months in an urban slum integrate child development services project I Delhi. Indian Pediatr 2002; 39: 136-144.
3. Seshadri S. Nutritional anaemia in south Asia. *In:* Malnutrition in South Asia: A Regional Profile. ROSA Publication No.5. UNICEF. November, 1997.
4. Draper A. Child Development and Iron Deficiency: the Oxford Brief. Washington DC: USAID, Opportunities for Micronutrient Interventions, and Partnership for Child Development, 1997.
5. Lozoff B, Jimenez E, Wolf AW. Long term developmental outcome of infants with iron deficiency. New Eng J Med 1991, 325: 687-694.
6. Dallman PR. Nutritional anemia of infancy. *In:* Nutrition during infancy. Eds. Tsang RC, Nichols BL eds. Philadelphia: Hanley and Belfus, 1988; pp 216-235.

7. Widdowson EM, Spray CM: Chemical development *in utero*. Arch Dis Child 1951; 26:205-214.
8. Simes MA, Salmenpera L, Perheentupa J. Exclusive breast-feeding for 9 months: risk of iron deficiency. J Pediatr 1984; 104: 196-199.
9. Ohls, RK. Evaluation and treatment of anemia in the neonate. In: Hematologic Problems of the Neonate, Christensen, RD (Ed), Philadelphia, WB Saunders, Philadelphia, 2000, p. 137.
10. Siimes MA. Iron nutrition in low birth weight infants. In: Stekel A, ed. Iron nutrition in infancy and childhood. New York: Raven Press, 1984: pp75-91.
11. Blot I, Diallo D, Tchemia G, Iron deficiency in pregnancy: effects on the newborn. Current Opinions Hematol 1999;6(2): 65.
12. Colomer J, Colomer C, Gutierrez D, Jubert A, Nolasco A, Donat J et al. Anaemia during pregnancy as a risk factor for infant iron deficiency: Report from the Vatican Infant Anemia Cohort (VIAC) study. Paediate Perinatal Epidemiol 1990; 4(2): 196.
13. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 1998; 47(RR-3):1.
14. Dallman PR, Siimes MA, Stekel A. Iron deficiency in infancy and childhood. Am J Clin Nutr 1980; 33: 86-118.
15. Pizarro F, Yip R, Dallman PR, Olivares M, Hertrampf E, Walter T. Iron status with different infant feeding regimens: relevance to screening and prevention of iron deficiency. J Pediatr 1991;118: 687-692.
16. Tunnessen, WW Jr, Oski, FA. Consequences of starting whole cow milk at 6 months of age. J Pediatr 1987; 111:813.
17. Pizarro F, Yip R, Dallman PR *et al*. Iron status with different infant feeding regimens: Relevance to screening and prevention of iron deficiency. J Pediatr 1991; 118: 687.
18. Ziegler EE, Fomon SJ, Nelson, SE *et al*. Cow milk feeding in infancy: Further observations on blood loss from the gastrointestinal tract. J Pediatr 1990; 116:11.
19. Calvo EB, Galindo AC, Aspres NB. Iron status in exclusively breast-fed infants. Pediatrics 1992; 90: 375.
20. Vuori E. Intake of copper, iron, manganese and zinc by healthy, exclusively breast-fed infants during the first 3 months of life. Br J Nutr1997; 42: 407-411.
21. Siimes MA, Vuori E, Kuitunen P: Breast milk iron: A declining concentration during the course of lactation. Acta Paediatr Scand 1979; 68:29-31.
22. Lonnerdal B, Keen CL, Hurley LS: Iron, copper, zinc and manganese in milk. Ann Rev Nutr 1981; 1:149-174.
23. Picciano MF, Guthrie HA: Copper, iron, and zinc contents of mature human milk. Am J Clin Nutr 1976; 29:242-254.

24. Celada A, Busset R, Gutierrez J *et al*. No correlation between iron concentration in breast milk and maternal iron stores. Helvetica Paediatrica Acta 1982; 37:11-16.

25. Zavaleta N, Nombera J, Rojas R *et al*. Iron and lactoferrin in milk of anemic mothers given iron supplements. Nutr Res 1995; 15:681-690.

26. Davidsson L, Kastenmayer P, Yuen M *et al*. Influence of lactoferrin on iron absorption from human milk in infants. Pediatr Res 1994; 35:117-124.

27. Abrams SA, Wen J, Stuff JE: Absorption of calcium, zinc, and iron from breast milk by five- to seven-month-old infants. Pediatr Res 1996; 39:384-390.

28. Brown KH, Dewey KG, Allen LH. Complementary Feeding of Young Children in Developing Countries: A Review of Current Scientific Knowledge. World Health Organization, Geneva, 1998.

29. Allen L, Casterline-Sabel. Prevalence and causes of nutritional anemias. *In:* Nutritional Anemias. Ed. Ramakrishnan U. CRC Press, NY, 2001; PP 7-21.

30. Ehrenkranz RA: Iron, folic acid and vitamin B_{12} . *In* Tsang RC, Lucas A, Uauy R, et al (eds): Nutritional Needs of the Preterm Infant: Scientific Basis and Practical Guidelines. Baltimore, Williams & Wilkins, 1993, pp 177-192

31. Feuillen YM. Iron metabolism in infants: II. Absorption of dietary iron. Acta Paedicatr 1954; 43:181-187.

32. Griffin I, Abrams SA. Part 2: Iron and breastfeeding. Pediatr Clin North Amer 2001; 48(2): 401-413.

33. Moe PJ. Normal red blood picture during the first three years of life. Acta Paediatr 1965; 54: 69-80.

34. World Health Organization Working Group on Infant Growth: An Evaluation of Infant Growth. Geneva, Nutrition Unit World Health Organization, 1994

35. Oski FA. Iron requirements of the premature infant. *In* Tsang RC (ed): Vitamin and mineral requirements in preterm infants. New York, Marcel Dekker, 1985, pp 9-21

36. Oski FA. Iron deficiency in infancy and childhood. New Engl J Med 1993; 329: 190-193.

37. Committee on Nutrition. Iron supplementation for infants. Pediatrics 1976; 58: 765-768.

38. Dallmen PR. Progress in the prevention of iron deficiency anemia in infants. Acta Pediatr Scand Suppl 1990; 365: 28-37.

39. Domellof M, Cohen RJ, Dewey KG, Hernell O, Rivera LL, Lonnerdal B. Iron supplementation of breastfed Honduran and Swedish infants from 4-9 months of age . J Pediatr 2001; 138(5) : 679-687.

40. Beaton GH and McCabe GP. Efficacy of intermittent iron supplementation in the control of iron deficiency anemia in developing countries .The Micronutrient Initiative, Canada, 1999.

41. Stoltzfus R, Dreyfuss M. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. INACG/WHO/UNICEF Report, 1998.

42. FAO/WHO. Report of a joint FAO/WHO expert consultation: requirements of vitamin A, iron, folate, and vitamin B 12. FAO Food and Nutrition Series No.23,1988.
43. Canada Health and Welfare. Nutrition recommendations: the report of the Scientific Review Committee. Ottawa: Ministry of Supply and Services,1990.
44. UNICEF/UNU/WHO/MI. Preventing iron deficiency in women and children. Technical Consensus on key issues. Boston MA and Ottawa, Canada: International Nutrition Foundation and the Micronutrient Intiative, 1999.
45. National Nutritional Anemia Control Programme. Policy on Control of Nutritional Anemia. Ministry of Health and Family Welfare, Government of India, 1991, pp 1-8.
46. Report. National Consultation on Control of Nutritional Anemia in India. Ministry of Health and Family Welfare. Government of India, 1998.
47. Brise H, Hallberg L. Effect of ascorbic acid on iron absorption. Acta Med Scand 1962, 171(Suupl): 51-58.
48. Reeves JD, Yip R. The lack of adverse side effects of oral ferrous sulphate therapy in one year old infants. Pediatrics 1985; 75: 352-355.
49. Abrams SA, O'Brien KO, Wen J *et al*. Absorption by 1-year-old children of an iron supplement given with cow's milk or juice. Pediatr Res 1996; 39:171.
50. Nelson SE, Ziegler EE, Copeland AM *et al*. Lack of adverse reactions to iron-fortified formula. Pediatrics 1988; 81:360.
51. Viteri FE. Control of iron deficiency anemia-New approaches. NFI Bulletin 1999; 20: 5-7.
52. Dubey AP, Rana M, Sachdev HPS, Choudhury P. Daily vs weekly supplementation in anemic children. Abstracts of Papers, 5th International Congress of Tropical Pediatrics, Jaipur, Feb 10-15, 1999.
53. Choudhury P. Prevention and strategies for control of iron deficiency anemia. *In*. Nutrition in Children: Developing Country Concerns. Eds Sachdev HPS, Choudhury P. New Delhi, Cambridge Press, 1994, PP. 236-244.
54. Geisser P. Properties and pharmacokinetics of iron salts and iron complexes. Research Department. Hausamann Laboratories. INC, Switzerland.
55. Jacobs P. Oral iron therapy in human subjects: comparative absorption between ferrous salts and iron poly maltose. J Medicine 1984; 3: 387-377.
56. Langstaff RJ, Geisser P, Heil WG, Bowdler MA. Treatment of iron deficiency anemia: A lower incidence of adverse effects with Ferrum Hausmann than ferrous sulphate. Brit J Clin Res 1993; 4: 191-198.
57. Jacobs P, Wood L, Bird AR. Better tolerance pf iron polymaltose complex compared with ferrous sulphate in the treatment of anemia. Haematology 2000; 5: 77-83.
58. Nestel P, Alnwick D. Iron/Multi-micronutrient supplements for young children. Summary and conclusions of a consultation held at UNICEF, Copenhagen, August 19-20, 1996, Washinton DC: OMNI/USAID 1997.
59. Zlotkin SH, Arthur P, Antwi KY, Yeung G. Randomized controlled trial of single versus three times daily ferrous sulphate drops for treatment of anemia. Pediatrics 2001; 108: 613-616.
60. Zlotkin SH, Arthur P, Antwi KY, Yeung G, Treatment of anemia with microencapsulated ferrous fumarate plus ascorbic acid supplied as ‘sprinkles’ to complementary (weaning) foods. Am J Clin Nutr 2001; 74:791-795.
61. Zlotkin S. Current issues for the prevention and treatment of iron deficiency anemia. Indian Pediatr 2002; 39: 125-129.

62. Report. Study of existing system of procurement, distribution and management of drugs under the national nutritional anemia prophylaxis programme and the national programme for prevention of nutritional blindness due to vitamin A deficiency in selected states of India. Unon Ministry of Health and Family Welfare, Govt. of India. 1991.
63. ACC/SCN. What Works? A Review of the Efficacy and Effectiveness of Nutrition Interventions, Allen LH and Gillespie SR, Manila, 2001, p.49.
64. Gomber S, Kumar S, Rusia U, Gupta P, Agarwal KN, Sharma S. Prevalence and etiology of nutritional anaemias in early childhood in an urban slum. Indian J Med Res 1998; 107: 269-273.
65. Casterline JE, Allen LH, Ruek MT. Vitamin B12 deficiency is very prevalent in lactating Guatemalan Women and their infants at three months postpartum. J Nutr 1997; 127: 1966-1972.
66. Stevens D, Burman D, Strelling MK, Morris A. Folic acid supplementation in lowbirth weight infants. Pediatrics 1979; 64: 333-335.
67. Wickramasinghe SN. Morphology, biology and biochemistry of cobalamin and folate deficient bonemarrow cells. Baillere's Clin Haemat 1995; 8: 441.
68. Worthington-White DA, Behenke M, Gross S. Premature infants require additional folate and vitamin B12 to reduce the severity of anemia of prematurity. Am J Clin Nutr 1994; 60: 930
69. Nutrient requirements and recommended dietary allowances for Indians. A report of the expert group of the Indian Council of Medical Research. New Delhi. Indian Council of Medical Research, 1990.
70. Indian Council of Medical Research. Dietary guidelines for Indians. – A manual, National Institute of Nutrition, Indian Council of Medical Research, 1998.