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A Randomized Placebo-controlled Trial of Iron Supplementation in Breastfed Young Infants Initiated on Complementary Feeding: Effect on Haematological Status

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ABSTRACT

To combat iron deficiency manifesting around six months of age, iron-fortified complementary feeding has been recommended. In developing countries, in view of the poor bioavailability of iron from predominantly cereal-based diets and the high cost of fortification, medicinal iron supplementation is an alternative intervention. This double-blind randomized placebo-controlled trial was conducted from April 1999 to March 2000 in the Out-patient Department of a tertiary hospital in New Delhi, India, to evaluate the haematological effects of medicinal iron supplementation to breastfed young infants initiated on complementary feeding. One hundred healthy non-low birth-weight, predominantly breastfed infants aged 4-6 months were randomized into two groups to receive either iron (2 mg/kg/day) (IS group; n=49) or placebo drops (P group; n=51) beginning with the initiation of home-based non-fortified complementary feeding. Haematological parameters and anthropometry of mothers and infants were measured at baseline and repeated for infants after four and eight weeks of recruitment. Seventy-one subjects (35 in the IS group and the 36 in P group) came for the first follow-up, and of these, 43 (19 in the IS group and 24 in the P group) reported for the second visit. The adjusted (for maternal and baseline infant ferritin) serum ferritin levels were significantly higher in the IS group at both the follow-ups (p=0.006). The adjusted (for maternal ferritin and baseline infant ferritin) change in haemoglobin was significantly higher only at the second follow-up (0.7 g/dL; 95% confidence interval [CI] 0.3-1.0 g/dL). The adjusted rise in haemoglobin was higher in initially anaemic infants (at second follow-up by 1 g/dL; 95% CI 0.5-1.6 g/dL). Medicinal iron supplementation, at the time of initiating complementary feeding, to breastfed young infants resulted in an elevation of serum ferritin and haemoglobin. The response was higher in initially anaemic infants. From a programmatic perspective, evidence needs to be generated on the relative merits of selective (anaemic) versus general supplementation and daily versus weekly supplementation.

***Key words*:** Iron; Iron deficiency; Anaemia, Iron-deficiency; Complementary feeding; Infant; Double-blind method; Randomized controlled trials; India

INTRODUCTION

Anaemia caused by iron deficiency is a major public-health problem (1). In India, the prevalence of anaemia is estimated to be 71% in urban and 76% in rural areas (2). Iron deficiency usually starts manifesting around the age of six months. This has been correlated to the depletion of iron stores (3) and the introduction of complementary foods (4) (rich in dietary inhibitors, such as phytates, tannates, etc.), particularly in a developing country.

Evidence indicates an adverse impact of iron deficiency on cognition (5) and motor development (6) and their reversibility with iron supplementation. Theoretical calculations based on the usual weaning diets suggest

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that iron is a problem micronutrient for meeting the recommended daily allowance (RDA) in this age group (7). These theoretical assumptions and the reversible adverse consequences of iron deficiency in infancy have led to advocacy for iron-fortified complementary feeding or iron supplementation, commencing with the introduction of complementary feeds, to young infants up to the age of three years.

Data in support of the latter recommendation are limited since the earlier controlled trials of iron supplementation to young infants have either not provided details of dietary intake or have not specifically commenced with the initiation of complementary feeding (8-15). There is a need to evaluate the effect of iron supplementation commencing, with the introduction of non-iron-fortified complementary foods, to healthy, term, breastfed infants aged 4-6 months. Limited information on the subject is available especially in India, where the bioavailability of iron from traditional cereal-based vegetarian complementary diets (rich in dietary inhibitors of iron absorption) is expected to be low, and the affordability of iron-fortified formulas is doubtful. We, therefore, conducted the current trial to evaluate the effect of an alternative of medicinal iron supplementation, commencing with the initiation of complementary feeding, to breastfed infants.

MATERIALS AND METHODS

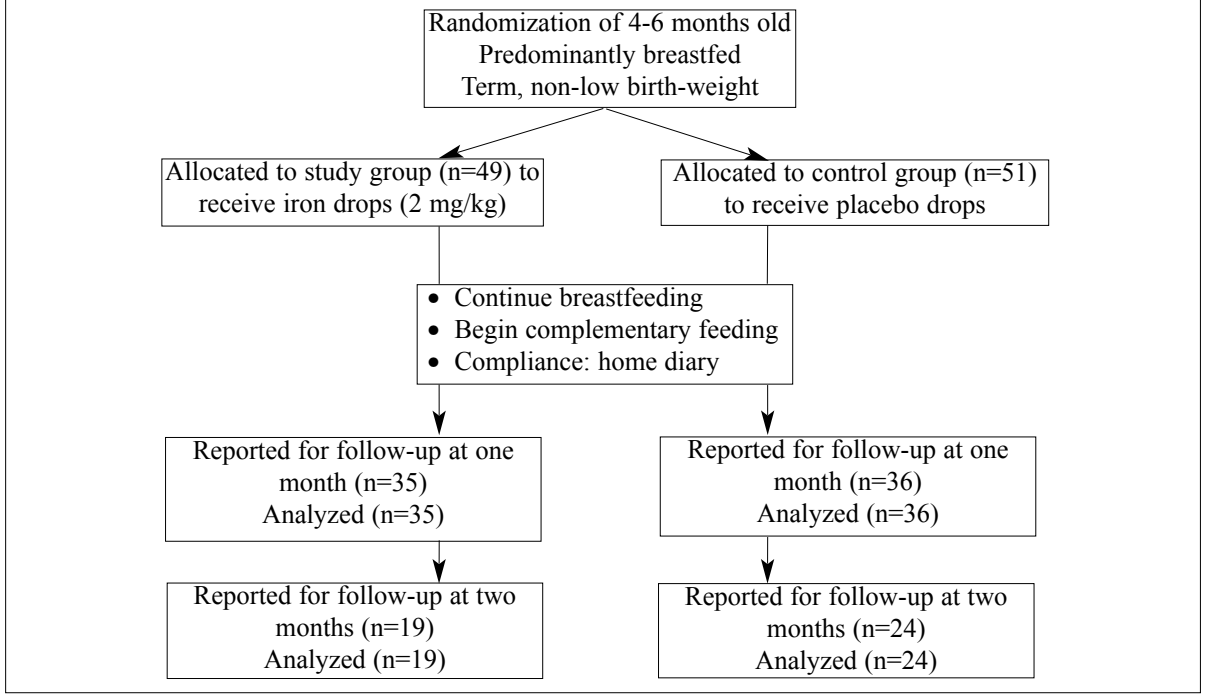
This double-blind randomized placebo-controlled trial of iron supplementation was conducted from April 1999 to March 2000 in the Out-patient Department of a tertiary hospital in New Delhi, India, situated at an altitude of 210 metres. The hospital primarily caters to an urban lower to lower-middle socioeconomic population. One hundred apparently healthy and predominantly breastfed infants (exclusive breastfeeding with occasional sips of water) aged 4-6 months were recruited on two prefixed days in a week. These infants were recruited after recovery from a minor ailment (such as upper respiratory infection) or were called at four months of age after vaccination (at 3½ months). They were of full-term gestation (37-41 weeks) with a birth-weight of >2,500 g. This was verified from the records for institutional and extra-institutional births (conducted in other institutions or nursing homes). The following infants (see the exclusion criteria) were excluded from the study: (i) twins, (ii) congenital malformation, (iii) history of blood transfusion, (iv) blood sampling (>10 mL) prior to recruitment, (v) infants already receiving iron supplementation, (vi) adverse neonatal events requiring admission to the special newborn care nursery, and (vii) those with significant current morbidity.

The institutional ethical committee approved the study. An informed verbal consent was obtained prior to recruitment.

At recruitment, the subjects were randomized into two groups based on random numbers generated by the computer (Fig.). The study group received iron in the form of medicinal drops (ferric ammonium citrate; 25 mg/mL) at the dose of 2 mg/kg/day, while the control group received a placebo solution identical to iron drops in colour, taste, and external appearance. Simultaneously, mothers were counselled to initiate complementary feeding (3-4 times a day) as per prevalent recommendations (16) with locally-available and home-made foods, such as banana, *khichri* (rice-pulse gruel cooked in oil), and *dahlia* (wheat cooked in milk). These natural foods were not supplemented or fortified with iron or other haematinic preparations. Both the groups were also advised to continue breastfeeding during the entire follow-up. Follow-up visits were advised after four and eight weeks of recruitment. Compliance of medicinal (iron or placebo) intake and feeding status were evaluated at each visit from a home diary maintained by the mother and verified by the amount of syrup leftover in the bottle. The drug intake estimated from the bottle and diary was similar.

A standard pre-tested proforma was used for recording baseline information, including antenatal and neonatal profiles, with emphasis on feeding history, birth-weight, and gestation. The dietary intake of infants was quantified by the 24-hour recall method (semi-quantitative estimates using home measures), and the calories were calculated as per values available for Indian foods (17). Maternal and infant weights, height/length, and current and interval morbidity (between two follow-up periods) were also recorded. The baseline haematological parameters evaluated included maternal haemoglobin and ferritin, and infant haemoglobin, peripheral smear, and serum ferritin. Haemoglobin was measured by the HemoCue system, which has been validated compared with other techniques (18). Serum ferritin was estimated using the MAGIWELL™ ferritin quantitative ELISA test kit. Maternal iron status was evaluated at baseline to control for its confounding effect on infant iron stores.

Fig. Summary of study design



Infant haemoglobin comprised the primary outcome variable, while serum ferritin, peripheral smear, and anthropometry (weight, length, and head circumference) were secondary outcome measures. These were evaluated at baseline and at the first and second follow-ups.

The primary outcome variable for sample-size consideration was infant haemoglobin. Based on earlier data from this institution in this age group (haemoglobin change SD of 1.23 g/dL), it was estimated that 25 infants would be required in each group to evaluate a difference of 1 g/dL of change in haemoglobin between the two groups after one month of supplementation with 95% confidence and 80% power. To account for potential loss to follow-up, double this number was recruited. Post-trial estimates of the power using the available sample size at one month of follow-up indicated that the study could detect a difference of 0.5 g/dL in haemoglobin with 95% confidence and 80% power.

Data entry was done on the computer using EpiInfo software. Analysis was performed on EpiInfo and SPSS software. The randomization code was broken after data entry and analysis. Serum ferritin was converted to natural logarithm to normalize the data. The various parameters in two groups were compared by Student's *t*-test, chi-square test, Fisher's Exact test, and Mann-Whitney test, wherever applicable. Additional statistical techniques included Pearson's correlation coefficient and multiple linear regression analysis.

RESULTS

In total, 100 infants who fulfilled the recruitment criteria were enrolled for the prospective follow-up (49 in the iron-supplemented group and 51 in the placebo group). Seventy-one of the recruited infants (35 in the iron-supplemented group and 36 in the placebo group) reported for follow-up after one month. At the second follow-up (two months after recruitment), 43 of the 71 infants at first follow-up (19 in the iron-supplemented group and 24 in the placebo group) were available. The baseline characteristics of infants reporting for and lost to follow-up were comparable (data not presented) at first follow-up. Similarly, infants who reported for the second follow-up were comparable to those who were lost between the first and the second follow-up (data not presented). The evaluated baseline maternal and infant characteristics (Table 1) and the quantity of complementary diet consumed (Table 2) were comparable in the two groups. However, the amount of complementary diet intake at the second follow-up was greater than that at the first follow-up. The compliance of drug intake

was comparable in the two groups (95% in the iron group and 91 % in the placebo group).

Table 1. Comparison of baseline characteristics [mean±SD or number (%)]

Characteristics	Iron-supplemented group (n=35)	Placebo group (n=36)
Maternal		
Age (years)	26.1±2.9	27.4±2.8
Weight (kg)	50.2±4.3	50.7±6.6
Height (cm)	152.2±4.9	151.9±6.3
Haemoglobin (g/dL)	12.1±1.4	12.1±1.3
Ferritin (mg/L; geometric mean)	15.1±2.9	14.9±3.0
Gravida	2.3±0.9	2.9±1.0
Place of delivery: hospital	21 (60.0)	16 (44.4)
Mode of delivery: vaginal	34 (97)	35 (97)
Gestation (weeks)	38.8±0.9	39.0±0.9
Antenatal haemoglobin estimation	4 (11.4)	2 (5.6)
Iron supplementation		
Number	6 (17.14)	0 (0)
Duration (weeks)	12±4.1	0 (0)
Dietary pattern: vegetarian	15 (42.8)	14 (38.8)
Infant		
Age (days)	148.2±18.5	148.6±18.5
Males	19 (54.3)	22 (61.1)
Birth-weight (g)	2719±190	2763±226
Birth length (cm)	48.9±1.3	49.4±1.1
Birth head circumference (cm)	34.0±0.8	34.3±0.8

None of the differences between the groups were statistically significant (p>0.05)

Table 2. Complementary food intakes at follow-up visits [mean±SD]

Complementary food	Iron-supplemented group (n=35)	Placebo group (n=36)
First follow-up		
Calories (kcal)	81.9±39.0	82.1±39.4
Cereals (g)	18.5±14.2	14.5±7.5
Pulses (g)	5.8±5.6	7.8±5.8
Vegetables (g)	5.2±5.9	4.7±5.6
Second follow-up		
Calories (kcal)	152.7±42.7	161.0±47.1
Cereals (g)	30.0±10.6	32.9±11.9
Pulses (g)	11.8±8.2	13.4±11.7
Vegetables (g)	13.4±8.3	15.6±14.6

None of the differences between the two groups were statistically significant (p>0.05)

At the first follow-up, serum ferritin was significantly higher in the iron-supplemented group (23.8 [2.6] µg/dL vs 11.8 [3.0] µg/dL; p=0.006), while the haemoglobin levels were comparable (Table 3). At the second follow-up, significantly higher values were observed for haemoglobin (11.5 [0.8] g/dL vs 10.8 [0.9] g/dL; p=0.009) and serum ferritin (30.6 [2.2] µg/dL vs 8.7 [3.2] µg/dL; p<0.005) in the iron-supplemented group.

The following relevant significant correlates were identified: baseline infant haemoglobin (from baseline to second follow-up) (r=0.607; p<0.001), baseline infant haemoglobin and ferritin (r=0.266; p=0.007), and baseline infant ferritin and maternal ferritin (r=0.408; p=0.009).

In view of the above correlations and the possible confounding due to maternal iron status, multiple regression analysis was performed by the enter method with change in haemoglobin as the dependent variable (at both the follow-ups) and treatment group, maternal ferritin, and baseline infant haemoglobin as independent variables. The baseline infant haemoglobin was entered in the model either as a continuous or a dichotomized (≤11 g/dL or >11 g/dL) variable (Table 4). At the first follow-up, there was no significant difference in the change in haemoglobin between the two groups, whereas at the second follow-up the iron-treated subjects had a significantly (p=0.001) higher change in haemoglobin (mean change adjusted for maternal ferritin and baseline infant haemoglobin as a continuous variable -0.7 g/dL; 95% CI 0.3-1.0 g/dL). At both the follow-ups, lower baseline infant haemoglobin was a significant (p=0.001) predictor of a greater rise in haemoglobin; at the second follow-up, the adjusted mean haemoglobin rise in initially anaemic infants (haemoglobin ≤11 g/dL) was higher by 1 g/dL (95% CI 0.5-1.6 g/dL). Similarly, at both the follow-up visits (data not depicted in Table 4), the serum ferritin levels adjusted for baseline infant ferritin and maternal ferritin values were significantly greater in the iron-supplemented group (first follow-up -ß=1.71, 95% CI 1.17-2.48, p=0.006; second follow-up -ß=3.25, 95% CI 2-5.28, p<0.001).

There was no statistical difference in reported interval morbidity in the two groups (Table 5). However, black colouring of the stools was significantly higher in the iron-supplemented group (90.7% vs 1.6 %, p<0.001).

DISCUSSION

Iron-deficiency anaemia is currently recognized to be the most widespread micronutrient deficiency. Pregnancy and infancy have been identified as the two core areas of attention for preventive planning. Efforts in infancy in this context have largely focused on iron-fortified foods, including formula (8-11). Many such studies have shown benefit in terms of the iron status of the infant. However, the utility of fortified foods, particularly, in the Indian setting may be limited because of poor affordability and predominantly cereal-based nature of usual complementary foods, which hinder iron bioavailability. The present study was, therefore, designed to evaluate the haematological effect of medicinal iron supplementation to infants being initiated on non-fortified usual complementary diets.

This hospital-based study had a high drop-out rate (57% at second follow-up). The possible reasons contributing to this could be: (i) Reporting from a distance to the hospital for follow-up with no reimbursement for transportation and loss of wages; (ii) Lack of perceived benefit of medication in apparently healthy children; (iii) Prolonged duration of medication; (iv) Blood letting at each contact; and (v) Poor educational and socioeconomic status. It would also be useful to examine to the extent feasible whether the exclusion of

Table 3. Comparison of outcome measures at follow-up visits [mean±SD or number (%)]

Variable	Haemoglobin (g/dL)	Serum ferritin (µg/dL)*	Peripheral smear			Head circumference (cm)	Weight (g)	Length (cm)
			NCHC	MCHC	NCNC			
Infants available at first follow-up (n=71)								
Baseline characteristics								
IS group (n=35)	11.3±1.5	22.3±2.7	24 (68.6)	9 (25.7)	2 (5.7)	41.3±0.9	5,686±574	61.3±2.7
P group (n=36)	10.9±1.2	16.1±8.1	27 (75.0)	6 (16.7)	3 (8.3)	41.2±1.1	5,694±628	62.2±2.8
p value	0.213	0.190†		0.618		0.727	0.955	0.192
Outcome measures at first follow-up								
IS group (n=35)	11.3±1.1	23.8±2.6	9 (25.7)	0	26 (74.3)	42.3±0.9	6,083±569	63.1±2.7
P group (n=36)	10.9±0.9	11.8±3.0	6 (16.7)	3 (8.3)	27 (75.0)	42.2±0.9	6,075±624	62.7±2.7
p value	0.11	0.006†		0.164		0.70	0.954	0.27
Change in outcome measures from baseline to first follow-up								
IS group (n=35)	0.0±0.9	2.0±29.3		-		1.0±0.2	425±368	1.76±1.14
P group (n=36)	0.0±0.7	-8.1±22.2		-		1.0±0.2	380±244	1.61±0.79
Mean difference (95% CI)	0.0 (-0.4 to 0.4)	10.2 (-2.2 to 22.4)		-		0.0 (-0.11 to 0.11)	45± (-102 to 192)	0.15 (-0.31 to 0.61)
p value	0.96	0.184†		-		0.99	0.54	0.48
Infants available at second follow-up (n=43)								
Baseline characteristics								
IS group (n=19)	11.1±1.1	24.8±2.7	3 (15.7)	1 (5.2)	15 (78.9)	41.3±1.1	5,611±633	61.5±3.2
P group (n=24)	11.2±1.7	19.8±3.1	4 (16.6)	1 (4.2)	19 (79.1)	41.2±1.0	5,806±660	62.6±2.7
p value	0.737	0.534†		0.983		0.484	0.334	0.267
Outcome measures at second follow-up								
IS group (n=19)	11.5±0.8	30.6±2.2	4 (21.1)	0	15 (78.9)	43.3±0.9	6,337±644	64.6±3.3
P group (n=24)	10.8±0.9	8.7±3.2	4 (16.6)	2 (8.3)	18 (75.0)	43.1±0.9	6,509±99	65.8±2.7
p value	0.009	0.002†		0.420		0.310	0.371	0.194
Change in outcome measures from baseline to second follow-up								
IS group (n=19)	0.3±1.3	3.3±37.1		-		2.0±0.3	778±532	3.08±1.52
P group (n=24)	-0.3±0.4	-18.9±34.7		-		1.9±0.4	703±341	3.26±1.54
Mean difference (95% CI)	0.6 (-0.1 to 1.2)	22.1 (3.1 to 41.3)		-		0.04 (-0.16 to 0.26)	75 (-195 to 345)	0.17 (-1.12 to 0.74)
p value	0.11	0.005†		-		0.65	0.57	0.71

* Means indicated are geometric means, except those depicted under change in outcome measures (arithmetic means)
† Calculated by Mann-Whitney ranking test
IS group=Iron-supplemented group
MCHC=Microcytic hypochromic
NCHC=Normocytic hypochromic
NCNC=Normocytic normochromic
P group=Placebo group

subjects not reporting for follow-up may have biased the findings. The feasible comparisons do not support this possibility: (i) None of the baseline characteristics were significantly different between those reporting and lost at the first and the second follow-ups; (ii) Proportion of subjects lost to follow-up in both the groups was statistically comparable; and (iii) Interval morbidity in the two groups at first or second follow-up was not statistically different. However, it is acknowledged that all characteristics with the potential to bias the results could not be examined for comparability.

Table 4. Multiple regression models of change in infant haemoglobin

Variable	b	SE (b)	95 % CI for b	p value	R^2	F-test: p value
First follow-up (n=71)						
Baseline infant haemoglobin as continuous variable						
Constant	3.727	0.669	2.393 to 5.061	<0.001		
Maternal ferritin (natural log)	0.087	0.069	0.050 to 0.224	0.209	0.385	<0.001
Baseline infant haemoglobin	-0.352	0.056	-0.463 to -0.241	<0.001		
Group (0=Iron,1=Placebo)	-0.130	0.148	-0.425 to 0.165	0.382		
Baseline infant haemoglobin as dichotomous variable						
Constant	-0.522	0.247	-1.015 to -0.028	0.038		
Maternal ferritin (natural log)	0.103	0.077	-0.051 to 0.257	0.187	0.223	0.001
Baseline infant haemoglobin (1=>11 g/dl,0=≤11 g/dL)	-0.708	0.169	-0.371 to -1.045	<0.001		
Group (0=Iron,1=Placebo)	-0.141	0.168	-0.476 to 0.194	0.404		
Second follow-up (n=43)						
Baseline infant haemoglobin as continuous variable						
Constant	6.385	0.854	4.658 to 8.112	<0.001		
Maternal ferritin (natural log)	0.173	0.083	0.005 to 0.341	0.044	0.673	<0.001
Baseline infant haemoglobin	-0.582	0.072	-0.727 to -0.437	<0.001		
Group (0=Iron,1=Placebo)	-0.662	0.191	-1.049 to -0.275	0.001		
Baseline infant haemoglobin as dichotomous variable						
Constant	-0.581	0.383	-1.356 to 0.193	0.137		
Maternal ferritin (natural log)	0.210	0.116	-0.026 to 0.446	0.079		
Baseline infant haemoglobin (1=>11 g/dL, 0=≤11 g/dL)	-1.042	0.275	-0.485 to -1.599	0.001	0.357	<0.001
Group (0=Iron,1=Placebo)	-0.731	0.271	-1.280 to -0.183	0.010		

b=Regression coefficient
CI=Confidence interval
Hb=Haemoglobin
SE (b)=Standard error of b

Table 5. Comparison of reported side-effects and morbidity experienced in two groups at follow-up [number (%)]

Side-effect/morbidity	Iron-supplemented group	Placebo group
First follow-up	(n =35)	(n=36)
Stool colour (black)*	32 [91.4]	1 [2.8]
Current morbidity	0	0
Interval morbidity†	2 (D, U) [5.7]	1 (M) [2.8]
Second follow-up	(n=19)	(n=24)
Stool colour (black)*	17 [89.4]	0
Current morbidity	0	0
Interval morbidity†	1 (D) [2.9]	2 (D) [5.6]

*p<0.001
†Refers to morbidity suffered in the period between the current and the last visit
D=Diarrhoea; M=Meningitis; U=Upper respiratory infection

The adjusted serum ferritin levels were significantly higher in the iron-supplemented group at both the follow-ups. However, at the first follow-up, there was no significant difference in the adjusted change in haemoglobin between the two groups, whereas at the second follow-up, iron-treated subjects had a significantly (p=0.001) higher adjusted change in haemoglobin (0.7 g/dL; 95% CI 0.3-1.0 g/dL). The haemoglobin response was greater in infants with lower baseline haemoglobin; the adjusted haemoglobin rise in initially anaemic subjects was 1 g/dL higher at the second follow-up.

The haemoglobin rise in the present study is in consonance with available literature in this age group. The

mean haemoglobin advantage in the iron-supplemented group in the available studies ranged from 0.4 to 0.8 g/dL over a follow-up period of 2-12 months when iron was given to all infants irrespective of their baseline iron status (4,9-14). In a recent study of iron supplementation (1 mg/kg/d) of breastfed Honduran (n=131) and Swedish (n=101) infants aged 4-9 months, a mean haemoglobin rise of 0.5 g/dL was demonstrable after two months. This benefit was greater after five months of supplementation (mean=0.6 g/dL) especially in the Honduran population (0.9 g/dL) (12). In a trial in Turkey on 113 infants [Group I=1 mg/kg/d (n=30); Group II=2 mg/kg/d (n=30); Group III=2 mg/kg/d on alternate days (n=30); group IV=placebo (n=23)], a haemoglobin benefit of 0.30 to 0.4 g/dL ($p<0.001$) was documented after four months in the iron-supplemented groups (13). The relatively poor rise in haemoglobin may be explained by the exclusion of all subjects with evidence of iron deficiency at recruitment (Hb <9.5 g/dL, MCV<74 fl and ferritin <12 ng/mL) in this study. We do not have comparable data from the other two reports (8,11) to comment on their timing of haemoglobin rise. The change in haemoglobin observed in anaemic subjects in the present study (1.5 g/dL using 2 mg/kg for 2 months) was also similar to the results of studies conducted in Ghana (1.4 g/dL using 4.5-6 mg/kg for 2 months) and Costa Rica (3.4 g/dL using 6 mg/kg for 6 months) (14,15). One study in England did not document any difference in haemoglobin between the iron-supplemented and the placebo group (10).

The dose of iron supplementation is an important factor that could have influenced the magnitude of the haemoglobin rise. Assuming a low or medium bioavailability of iron from the initiated complementary diet (*khichri* and *dahlia* which are prominently cereal-based) with breastfeeding, the iron requirement from complementary foods has been estimated to be about 21 and 11 mg respectively (7). With an average weight of 5.5 kg at the time of initiation of complementary feeding, this translates to a daily supplementation of 2 mg/kg, the dosage used by us. This supplementation dose is marginally higher than formula-feed iron-fortification trials in which the extrapolated average iron intakes were 0.6-1.3 mg/kg (4,8,11). The corresponding estimates for medicinal iron drops were 1 and 2 mg/kg/day in two trials cited earlier (12,13). The bioavailability of iron in these trials could have been higher because of the nature of complementary diets.

In the present study, significant differences in serum ferritin concentrations were obtained at the first (12.7 µg/dL) and the second follow-up (22.0 µg/dL) between the iron-supplemented and the placebo groups. The rise in serum ferritin concentration, thus, preceded the rise in haemoglobin. Other trials in this age group by Domellof *et al*. (mean 29 µg/dL higher after two months using 1 mg/kg/day) and Ermis *et al*. (12,13) (mean 23.2 µg/dL higher after five months using 2 mg/kg/day) also recorded similar differences in serum ferritin with iron supplementation. The study conducted in England, which did not document a significant change in haemoglobin, also did not record a significant difference in serum ferritin after one year of supplementation (10).

The present study failed to show any significant difference in anthropometry at either first or second follow-up. Similar observations were documented in other trials reporting on anthropometry (3,10). However, in the Honduras study, an inverse correlation between gain in infant weight from birth to six months and ferritin concentration at six months was obtained (4). Other studies evaluating the impact of iron supplementation on growth parameters in the past have been predominantly carried out in preschool and older children. These trials have yielded equivocal results with some studies showing benefit (9,19) which the others failed to support (10,20,21). The follow-up period and the sample size in the present trial were inadequate to estimate the anthropometric differences. A sample size of 50 subjects in each group was required to detect a difference of 168 g with 95% confidence and 80% power.

The iron supplements were generally well-tolerated, and no infants reported any side-effects during the study period. A substantial proportion (32/35) in the iron-supplemented group reported black-coloured stools, a documented effect of iron intake. The recorded interval morbidity experience of the two groups was similar. A recent systematic review has concluded that iron supplementation has no apparent harmful effects on the overall incidence of infectious illnesses in children, although it slightly increases (11%) the risk of developing diarrhoea (22).

It is concluded that medicinal iron supplementation (2 mg/kg dose) in predominantly breastfed non-low birth-weight infants aged 4-6 months initiated on beginning complementary feeding (based on vegetarian diets) results in an improvement of serum ferritin and

haemoglobin (0.7 g/dL after two months; 95% CI 0.3-1.0 g/dL). The response is greater in initially anaemic infants. These results need to be validated in diverse settings with different complementary diets on larger sample sizes with better follow-up rates. Future trials should also aim to evaluate the functional consequences of such iron supplementation apart from haemoglobin, for example, cognition and psychomotor effects. Considering the high drop-out rates and greater response in anaemic infants, from a programmatic perspective, evidence needs to be generated on the relative merits of daily versus weekly supplementation and selective (anaemic infants) versus general supplementation.

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