Does maternal iron supplementation during the lactation period affect iron status of exclusively breast-fed infants?

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Iron deficiency anemia (IDA) causes growth and developmental retardation in infants. Iron supplementation from the 4th month of age may prevent IDA, but side effects of oral iron supplementation limit its usage. The aim of this study was to investigate the effect of maternal iron supplementation on the iron status of mothers and their exclusively breast-fed infants. In a prospective, placebo-controlled, double-blinded randomized study, healthy mothers (Hb≥11 g/dl) and their 10-20-day-old healthy term infants who were admitted to Hacettepe University for neonatal screening were enrolled. The mothers who were intending to exclusively breast-feed at least up to four months were included. Iron supplementation (n=82, 80 mg elementary iron) and placebo (n=86) were given to the mothers randomly for four months. The anthropometrical measurements of infants were recorded monthly. Of all, 69 mothers and their infants in the iron group and 63 in the placebo group completed the study. At the end of the study period, blood samples (complete blood count, serum iron, iron binding capacity and serum ferritin) were drawn from the mothers and their infants. After adjustment for baseline hemoglobin value, the mean levels of hemoglobin, serum iron and ferritin were similar in the two groups at the end of the study; however, serum iron binding capacity was significantly lower in the iron group than in the placebo group. Giving maternal iron supplementation during the first four months of the lactation period had no effect on the serum iron and ferritin levels of mothers and infants. This could be due to the relatively short duration of the follow-up period. A longer follow-up period is recommended to detect the effect of the maternal iron supplementation during lactation.

Key words: iron deficiency anemia, infant, breast-fed, maternal supplementation, iron.

A relationship is known to exist between iron deficiency and deficits in work productivity and child development, and between severe anemia and maternal and child mortality[1-4]. Although iron is essential for optimum development in infants and children, and iron deficiency anemia (IDA) affects behavioral, mental and motor development in the first year of life, delayed treatment of IDA did not improve mental development scores[2,3,5]. Although screening tests are recommended in infants at high risk of iron deficiency[6,7], they are expensive, have changing validity and are not always available[1,6,8]. Therefore, preventing iron deficiency is a key issue in infancy. Provision of iron supplements has been recognized as a key strategy for reaching target populations at high risk of iron deficiency[1,6]. However, bad taste of iron medication and side effects of iron supplementation including loss of appetite, nausea, vomiting, defecation problems and tooth pigmentation limit its usage during the infancy period[6,9].

A previous study in Hacettepe University İhsan Doğramacı Children's Hospital showed that anemia prevalence was 35.4% in infancy (2-24 mo) and the main cause was iron deficiency[10]. Also, in another study, 36% of infants were found to be anemic in the 6th month[11].

Considering the detection of more prevalent anemia in infancy and pregnant women, and the possibility of irreversible adverse effects of

anemia during the infancy period[1,8,12,13], the mother and infant couple should be protected from anemia. The iron status during pregnancy and the lactation period might affect the iron status of the exclusively breast-fed infant. Although the effects of prophylactic iron supplementation in pregnancy are well known, the effects of iron supplementation to mothers in the lactation period are not clear[8,14,15]. The aim of this study was to investigate the effect of maternal iron supplementation on the iron status of mothers and their exclusively breast-fed infants.

Material and Methods

This study was a prospective, placebo controlled, double-blinded and randomized intervention, conducted between 1 January and 31 September 2001 in Ankara, Turkey.

Mothers and their babies, 10-20 days of age, who were admitted to Hacettepe University İhsan Doğramacı Children's Hospital for neonatal screening were enrolled in the study if the babies were exclusive breast-fed and if it was intended to continue exclusive breast-feeding up to at least four months. Preterm (gestational age <37 weeks), low birth weight babies (birth weight lower than 2700 g), twins and babies with metabolic, renal or hepatic disease, or hyperbilirubinemia treated with phototherapy or exchange transfusion were excluded from the study. Also, mothers with complications during pregnancy like preeclampsia, vaginal bleeding, or anemia and who were being treated with any iron medication were not included in the study.

Study Plan: Parents willing to take part in the study were informed about the purpose and the nature of the study and a written consent was obtained. The Ethical Committee of the Faculty of Medicine, Hacettepe University, approved the study protocol (TBK 01/4-5).

At the beginning of the study, blood samples for complete blood count (CBC), serum iron (SI), serum iron binding capacity (SIBC) and serum ferritin (SF) were obtained from mothers. Mothers with hemoglobin level lower than 11 g/dl were excluded and the others were randomized into two groups according to their file number. The even-numbered group received OR1 (iron) and the odd-numbered group received OR4 (placebo) for four months.

Follow-up: Compliance with intervention was monitored. For the first two months, mothers were telephoned weekly and asked if they received their medication properly and exclusively breast-fed their babies. For the following two months, mothers were telephoned every two weeks. Mothers who received less than four pills per week were considered "noncompliant" and excluded from the study.

In the study, babies were examined monthly in the hospital. Their weight, height and head circumferences were recorded and their immunizations were done according to the schedule. Mothers were questioned regarding all possible side effects of medication and if present, these were recorded. After the fourth month of the intervention, blood samples were drawn from mothers and babies for CBC [hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), red cell distribution width (RDW)], SI, SIBC and SF.

Preparation of the Medication: Iron and placebo drugs were prepared by Koçak Drug Company. Both drugs had the same shape, color, and size. Placebo pills (Lot no: 00011001102) contained starch and iron pills (Lot no: 92612001202) contained 270 mg ferrous sulfate (80 mg of elementary iron).

Laboratory: Blood samples (4 ml) were collected from the mothers only at the enrollment and from both mothers and babies at the 4th month of the intervention. CBC analyses were done on a Coulter Counter-S model (Coulter®; STKS, Coulter Corp., Hialeah, FL, USA). Serum samples for SI, SIBC and SF were stored after centrifugation at –20^{o}C until analysis. Serum samples were analyzed at the end of the study. SI and SIBC were measured by colorimetric methods (Sigma) and SF by a commercial kit (Tina quant® a ferritin(e), Lot no: 62159101-62376101, Preciset ferritin(e), Lot no: 61043462, Roche, USA) with Modular Analytic System [(ROCHE Diagnostics/HITACHI (Modular DP), Japan)]. Transferrin saturation (TS) was calculated by (SI/SIBC) X 100.

Evaluation of Hematological Data: For mothers, anemia was defined as Hb<11 g/dl for the postpartum 10-20th days and mothers with this level were not taken into the study on admission. During the follow-up period, IDA was defined as Hb lower than 12 g/dl in combination with two of the following iron status indices being abnormal with

the following cut-off values: MCV<80 fl, SF<15 μg/L, SI<30 μg/dl and TS<16%. Mothers who had SF lower than 15 μg/L were classified as having iron deficiency[16]. In infants, iron deficiency was defined as SF<20 μg/L for 4-5 mo of age, and IDA was defined as Hb<9.5 g/dl in combination with two of the following: MCV<74 fl, SF<20 μg/L, SI<18 μg/dl and TS<7%[17].

If an infant or mother was detected to have IDA during the follow-up period, the infant-mother pair was subsequently withdrawn and referred for treatment.

Sample Size: A preliminary study in exclusively breast-fed infants who were five months of age (n=15) determined a mean Hb value of 11.2 g/dl (SD=0.4). Using this preliminary study, a pre-study analysis showed that a sample size of 63 infants per group was required (80% power; 5% significance level; two-tailed test) to detect a difference in Hb value of at least 0.2 g/dl among groups[18]. Assuming a dropout rate of 20%, we planned to recruit at least 80 infants for each group.

Statistical Analysis: In the study, the anthropometric and hematological parameters between groups were compared with Student's-t test. Hematological parameters at the end were analyzed by adjusting the baseline values. The difference of case distribution between the groups was analyzed by using chi-square test. Because values for SF approached a log normal distribution, geometric mean titer was used in all calculations. Statistical analyses were performed by using software package SPSS for Windows (SPSS Inc, Chicago, IL, USA).

Results

Descriptive Data of Subjects: At the beginning of the study, 181 mother and infant couples participated in the study; 13 mothers were determined as anemic (Hb<11 g/dl), and the remaining 168 were enrolled (Fig. 1). In the following period, 36 participants dropped

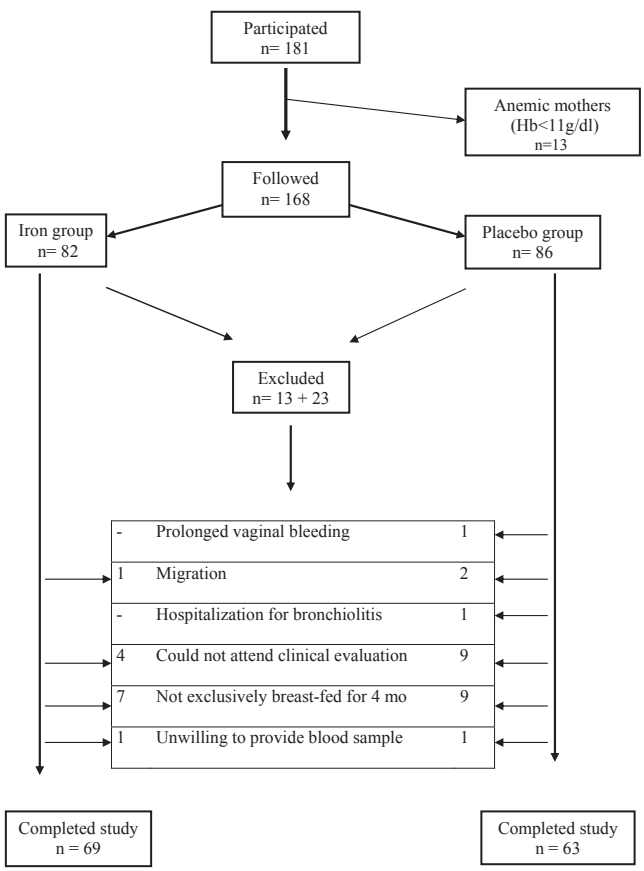

Fig. 1. Flow chart of the study and causes of exclusion.

out [not exclusively breast-feeding (n=16), could not attend clinical evaluation (n=13) or relocated to another city (n=3), unwilling to provide blood sample at the end (n=2), hospitalization for bronchiolitis (n=1), and prolonged postpartum bleeding for 1 month (n=1)]. Of all, 69 from the iron group and 63 from the placebo group completed the study. All remaining participants were included in the statistical analysis. The total dropout rate was not significantly different between iron and placebo groups. Both dropout and non-dropout groups were similar according to maternal age, gravidity, parity, average period of iron use in pregnancy, baseline Hb level, time since the previous pregnancy, gestational age, birth weight, sex and birth order.

Maternal age, gravidity, parity, average period of iron use in pregnancy, baseline Hb level, time since the previous pregnancy, gestational age, birth weight, sex and birth order were not significantly different between the iron and placebo groups (Table I).

Follow-up Period: Some complaints including constipation, diarrhea, abdominal pain, pigmentation in tooth or feces, dizziness, nausea or vomiting were detected in 24 iron-supplemented mothers (34.8%) and in 17 placebo-supplemented mothers (27.0%) (p>0.05, Table II).

In the follow-up period, weight, height and head circumferences of the children were similar between the two groups (p>0.05).

Table I. Baseline Characteristics According to Supplementation Groups*

		Iron group (n=69)	Placebo group (n=63)
Maternal			
Age (yr)**		27.8 ± 5.1	28.1 ± 4.6
Gravidity**		2.0 ± 1.5	1.8 ± 1.1
Parity **		1.6 ± 0.7	1.4 ± 0.6
Iron medication in the pregnancy period (mo)**		4.4 ± 2.4 (n=57)	4.0 ± 2.3 (n=57)
Time between the previous pregnancy (mo)**		55.5 ± 35.3 (n=34)	59.1 ± 33.7 (n=34)
≤24 mo	n (%)	7 (20.6)	6 (17.6)
>24 mo	n (%)	27 (79.4)	28 (82.4)
Baby			
Birth week**		39.4 ± 1.1	39.5 ± 1.1
Birth weight (g)**		3470 ± 431	3380 ± 377
Male/female n (%)		34/69 (49.2)	36/63 (57.1)
	1st child	40 (58.0)	39 (61.9)
Birth order n (%)	2nd child	22 (31.8)	21 (33.3)
	3rd or more	7 (10.1)	3 (4.7)

*p>0.05 for comparison between groups.
** Mean ± SD.

Table II. Distribution of Complaints According to Supplementation Group*

	Iron group		Placebo group	
Complaint	n	%	n	%
Constipation	9	13.0	10	15.8
Abdominal pain	7	10.0	3	4.7
Tooth/feces pigmentation	4	5.8	0	0
Nausea	1	1.4	2	3.2
Vomiting	1	1.4	1	1.6
Dizziness	1	1.4	1	1.6
Diarrhea	1	1.4	0	0
Total mothers with complaint	24	34.8	17	27.0

*p>0.05 for comparison between groups.

Hematological Data: Two mothers from iron group and one from placebo group were found to be iron deficient at the beginning of the study. At the 4th month of intervention one mother had iron deficiency and one had IDA; both were in placebo group and the iron-deficient mother was the one who was iron deficient on admission.

At the end of the study, 13 babies had iron deficiency [7 (10%) in iron group and 6 (9.5%) in placebo group ($p>0.05$)]. One baby (1.6%) in placebo group had IDA, but no baby in the iron group. Mothers of the children who had iron deficiency or IDA were not iron-deficient themselves.

Although the randomization was done on admission, there was a significant difference in the baseline hemoglobin level between the groups (Table III). To control the effect of maternal baseline Hb, the statistical analysis at the end of study was done by adjustment. At the 4th month of intervention, Hb, Hct and RDW values of mothers were similar in both groups. MCV was higher in the iron group ($p<0.05$). After the adjustment for maternal baseline Hb, only the mean level of SIBC of mothers and babies in the placebo group was significantly higher than that in the iron group ($p<0.05$, Table IV). However, iron-supplemented mothers had higher MCV

Table III. Baseline Hematological Parameters of Mothers

	Iron Group (n=69)	Placebo Group (n=63)	p
Hb (g/dl)*	12.9 ± 1.2	13.6 ± 1.2	0.001
Hct (%)*	38.9 ± 3.8	41.3 ± 3.5	0.001
MCV (fl)*	88.3 ± 6.4	89.6 ± 5.8	0.204
RDW (%)*	14.1 ± 2.0	13.7 ± 2.2	0.284
Iron (μg/dl)*	57 ± 31	73 ± 30	0.058
SIBC (μg/dl)*	394 ± 85	322 ± 48	0.219
TS (%)*	14.9 ± 8.7	18.5 ± 10.7	0.042
Ferritin (μg/L)**	41.6 (5.5-120.5)	44.9 (11.9-140.8)	0.293

*Mean ± SD.
**Geometric mean (min-max).
Hb: Hemoglobin. Hct: Hematocrit. MCV: Mean corpuscular volume. RDW: Red cell distribution width. SIBC: Serum iron binding capacity. TS: Transferrin saturation.

Table IV. Hematological Data of Mothers and Babies Adjusted for Baseline Maternal Hemoglobin, at the 4th Month of Intervention

	Iron Group (n=69)	Placebo Group (n=63)	p
Mothers			
Hb (g/dl)*	13.5 ± 0.1	13.3 ± 0.1	0.062
Hct (%)*	39.3 ± 0.3	38.6 ± 0.3	0.159
MCV (fl)*	85.0 ± 0.5	82.8 ± 0.5	0.002
RDW (%)*	12.8 ± 0.1	13.0 ± 0.1	0.238
Iron (μg/dl)*	73 ± 4	72 ± 4	0.790
SIBC (μg/dl)*	319 ± 7	353 ± 8	0.003
TS (%)*	23.6 ± 1.3	21.0 ± 1.3	0.551
Ferritin (μg/L)**	45.3 (15.0-166.6)	37.9 (11.7-364.5)	0.173
Babies			
Hb (g/dl)*	11.3 ± 0.1	11.6 ± 0.1	0.106
Hct (%)*	32.6 ± 0.3	33.3 ± 0.3	0.103
MCV (fl)*	77.1 ± 0.5	77.0 ± 0.6	0.834
RDW (%)*	11.8 ± 0.1	12.1 ± 0.1	0.144
Iron (μg/dl)*	40 ± 3	46.0 ± 3.94	0.118
SIBC (μg/dl)*	303 ± 7	330 ± 7	0.01
TS (%)*	13.8 ± 0.8	14.3 ± 0.9	0.624
Ferritin (μg/L)**	58.1 (13.6-262.0)	55.5 (6.8-207.5)	0.667

*Mean ± SD, **Geometric mean titers (95% CI). Hb: Hemoglobin. Hct: Hematocrit. MCV: Mean corpuscular volume. RDW: Red cell distribution width. SIBC: Serum iron binding capacity. TS: Transferrin saturation.

than placebo-supplemented ones. Other hematological parameters of mother-infant couples were similar between groups.

Discussion

In this study, we detected that Hb and iron status of mothers and babies were similar in iron- and placebo-supplemented groups at the 4th month of intervention. To our knowledge, this is the first clinical study investigating the effects of maternal iron supplementation on iron status of mothers and their exclusively breast-fed babies. Previously, Anaokar and Garry[19] studied the iron content of rat milk and status of lactating rats and their pups to investigate the relationships between the iron concentration of maternal diet and iron content of milk, and between the milk iron content and neonatal iron status. They found that rats fed with high-iron diet had pups with better iron status than the iron-deficient fed group[19]. But in our study, iron supplementation in lactating mothers did not have any significant effect on their or their babies' hematological status. One possible explanation for this was that mothers enrolled in the study did not have anemia at the beginning of the study, due to ethical considerations. Since these mothers were not iron deficient, it is possible that the iron content of their milk was already good and could not be improved by further iron administration, with no effect on iron status of babies. Another possible explanation is that the 4th month of intervention for follow-up blood sampling might be too early to detect the actual condition for iron status of the infant-mother couple. Blood was drawn at the 5th month of age (the 4th month of intervention) because most of the mothers ceased breast-feeding at that time and began to give additional food, and we wanted to detect the effect of maternal supplementation and iron status of infants before weaning. Similarly, Preziosi et al.[20] found no difference in iron status of newborns whose mothers had iron supplementation during the pregnancy period and those whose mothers took placebo; however, such difference was reported to appear at three months and persisted six months after delivery in that study. These data were consistent with those of Mac Phail et al.[21] who observed that infants of mothers who had received adequate iron supplementation had very low SF concentration at six months of age. Long-term follow-up of cases with maternal supplementation would show the efficacy of maternal iron supplementation.

At the 5th month of age, only 10.1% of the iron group and 9.5% of the placebo group had iron deficiency. Only 1.6% of placebo had IDA. However, frequency of IDA was found to be much higher (30-35%) in the previous studies done in our hospital[9-11]. We have two possible explanations for this change in frequencies. First, infants in this study were exclusively breast-fed until five months of age. Exclusive breast-feeding is one of the most well-known strategies for preventing anemia in the first 4-6 months of age[22]. Despite low iron content in breast milk, its bioavailability is higher and absorption rate of breast-milk iron is nearly 50-60%[23]. Second, the enrollment of non-anemic mothers at the beginning could also have some effect on the frequency of iron deficiency in mother-infant couples at the 5th month of age. Similarly, it was shown that maternal iron status was effective on the iron status of babies and that IDA or iron deficiency in pregnancy increases the risk of infant anemia[9,24,25]. In addition, Dömellof et al.[26] reported that iron supplementation of term breast-fed infants from 4-6 months to at least nine months of age could improve iron status and reduce anemia in socioeconomically disadvantaged populations where IDA is prevalent[26]. In that study, iron status of mothers was not known; however, mothers in socioeconomically disadvantaged populations might have higher prevalence of anemia. Breast-milk iron and body iron stores are the main iron depots for babies[21,25,27]. Together with previous studies, our study shows that breast-fed infants whose mothers do not have anemia at the postpartum 10-20 days do not need extra iron for 4-6 months. Thus, future studies should consider the value of screening of mothers at the postpartum 10-20 days on the prevention of IDA in infants.

A study conducted in Hacettepe University mentioned that 25 of 45 children (55.5%) who received iron suffered from side effects. In this study, two of the 12 excluded participants did not want to use medication because of its side effects[9]. In our study, medications were given to mothers and no adverse effects in babies due to maternal supplementation were reported.

In conclusion, iron supplementation to non-iron-deficient mothers in the lactation period from the 2nd week to 5th month had no statistically significant effect on iron status of infants and mothers at the 5th month. Further studies are needed in anemia-prevalent populations, and longer follow-up (more than four months, at least one year) may also provide more data about efficacy of maternal iron supplementation in the lactation period.

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