Effect on haematological and anthropometric parameters of iron supplementation in the first 2 years of life. Risks and benefits

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Effects of iron supplementation (IS) on haematological and anthropometric parameters in a cohort of 121 healthy children, followed from 6 to 24 months of life, in the Paediatric Department, Second University of Naples, were evaluated.
Children were randomly segregated in four groups: (1) exclusively breast feeding (BF) weaned with non-iron fortified (NIF) foods, (2) BF and iron fortified formulas (IFF) and foods, (3) exclusively IFF and foods, (4) BF and oral iron supplementation (OIS). Haematological parameters (Hb, MCV, Serum ferritin and transferrin saturation) in addition to anthropometric measurements (length and weight) were obtained.
Results from the study at 6, 12, 18 and 24 months showed significantly lower values of haematological parameters in BF infants than other groups and in IFF infants than in those with OIS. In contrast children with OIS showed significant lower length. It appears that IS may be of limited or no benefit for growth in non-iron deficient children.

Keywords: Iron supplementation, Anthropometric measurements, Haematological parameters, Iron fortified formulas, Oral iron supplementation

Introduction

Iron deficiency (ID) remains the must common nutritional deficiency worldwide.[1–3] Because of its high prevalence among infants and young children iron supplementation (IS) is recommended during these periods of increased requirement.[4,5]

Positive effects achieved with the introduction of baby foods iron fortified, particularly in children from populations with high anaemia prevalence as well as in children from poorest social groups, led to recommend its use worldwide.[4,5]

Iron represents an essential nutrient for all tissue in developing. However, the metal is characterized by prooxidant activity and, in excess, can generate free radicals, impairing normal cellular functions and enzymatic activity and can reduce the absorption of other essential nutrients.[6,7]

Recently some authors have pointed out that IS has been extended indiscriminately without assessing the real needs, benefits and possible risks, particularly in iron sufficient infants and children.[8,9]

Moreover, there is controversy over possible adverse effects of IS or iron fortified foods on growth and morbidity in iron sufficient infants and children.[8–11]

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The aim of the study is to examine the evidence for the health benefits and risks of preventive supplementation in a population of infants living in Italy/Campania region.

Materials and Methods

We studied over the past three years, in a cohort of 121 healthy children that were recruited during routine visits to the Paediatrics Department, Second University of Naples, the effects of iron suppementation on growth, evaluating haematological and anthropometric parameters. Informed consent was obtained from parents. Principles outlined in the Declaration of Helsinki were followed. Procedures followed were in accordance with the ethical standards.

Selection criteria were as follows: gestational age $\geqslant$37 weeks, birth weight >2500 g and no associated chronic illness.

Children were randomly recruited among those with oral iron supplementation (OIS) or iron fortified formulas (IFF) and foods and those breastfeeding without IS. They were evaluated at 6, 12, 18 and 24 months.

All infants were weaned between the 5th and 6th month of life.

They were segregated into four groups of comparison as follows:

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Table 1 Haematological and anthropometric parameters in infants at 6 months according to iron supplementation

	BF and NIFF foods		BF+IFF and foods		IFF and foods		BF+OIS	
	35 children		28 children		32 children		26 children	
	F(20) a	M(15) b	F (16) c	M(12) d	F(18) e	M(14) f	F(12) g	M(14) h
Hb(±DS) (g/dl)	11.1±0.5	11.2±0.4	11.4±0.6	11.7±0.5	11.6±0.4	11.6±0.2	11.8±0.3	11.7±0.4
MCV(±DS) (fl)	75.2±0.9	76.2±0.6	76.4±0.4	76.7±0.3	76.2±0.9	78.8±0.3	76.1±0.7	77±0.3
Weight(±DS) (kg)	6.8±0.21	7.2±0.24	7±0.6	7.3±0.8	7.1±0.9	7.2±0.1	7.2±0.9	7.2±0.8
Length(±DS) (cm)	64.6±1.35	67±1.2	64.5±1.3	67.1±0.3	64.3±1.6	67.2±1.5	63.9±1.3	67.1±0.6
Ferritin(±DS) (ng/ml)	15±1	15.2±1.1	18±0.9	18.2±0.5	17.9±1.5	18.2±2.1	17.2±0.9	20.2±0.5
TSI(±DS) (%)	14±1.5	15±1.2	16.5±0.9	17±0.7	20±1.1	18±0.9	18±1.5	22±0.8

Note: Hb $P<0.05$ a *vs* c, e, g; c *vs* g; $P>0.05$ c *vs* e; e *vs* g MCV $P<0.05$ a *vs* c, e, g; $P>0.05$ c *vs* e, g; e *vs* g Weight $P<0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g.
Hb $P<0.05$ b *vs* d, f, h; d *vs* f, h; $P>0.05$ f *vs* h MCV $P<0.05$ b *vs* d, f, h; $P>0.05$ d *vs* f, h; f *vs* h Weight $P<0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h.
Length $P>0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g Ferritin $P<0.05$ a *vs* c, e, g; c *vs* g; $P>0.05$ c *vs* e TSI $P<0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g.
Length $P>0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h Ferritin $P>0.05$ b *vs* d, f, h; d *vs* h; f *vs* h; $P>0.05$ d *vs* f TSI $P<0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h.

(i) exclusively breast feeding (BF) weaned with non-iron fortified (NIF) foods.
(ii) BF and IFF and foods.
(iii) Exclusively IFF and foods.
(iv) BF and OIS.

Infants that received OIS started supplementation from 4 to 9 months of life as a recommended prophylactic dose (1 mg of elemental iron kg/day) and the dose was adjusted monthly according to infant's weight.

The following haematological parameters have been recorded: Hb concentration, MCV, serum ferritin and transferrin saturation. Hb and MCV values were compared to the percentiles values for age and sex. Serum ferritin values >15 ng/ml and iron saturation >15% were considered normal.

Anthropometric measurements have been performed as follows: body weight by electronic scales, length by statometer. Body weight and length were calculated as standard deviation scores based on published normative data according to sex and age.[12]

Statistical analysis for comparison among groups was performed by ANOVA. Significant differences have been set at $P<0.05$.

Results

Haematological and anthropometric results of the study respectively reported at the age of 6, 12, 18 and 24 months are shown in Tables 1–4.

Our data show that at 6 months of age BF weaned with NIF foods infants show significant lower haematological parameters and weight than others, as well as BF and IFF and foods infants while non-significant differences of length were observed among the groups.

At 12 months of age BF weaned with NIF foods infants had haematological parameters significantly lower than other groups. Breast feeding and IFF infants showed also haematological parameters significantly lower than exclusively IFF and OIS groups, while non-significant differences of weight were observed among the groups. Length was significantly

Table 2 Haematological and anthropometric parameters in infants at 12 months according to iron supplementation

	BF and NIF foods		BF+IFF and foods		IFF and foods		BF+OIS	
	35 children		28 children		32 children		26 children	
	F(20) a	M(15) b	F (16) c	M(12) d	F(18) e	M(14) f	F(12) g	M(14) h
Hb(±DS) (g/dl)	11.6±0.3	11.5±0.4	11.7±0.4	12±1	12.2±0.6	12±0.6	12.5±0.5	12.6±1
MCV(±DS) (fl)	76.1±0.6	76.5±1.1	77.2±0.3	77.1±0.4	78.1±0.2	77.6±0.4	79.2±0.9	79.9±0.4
Weight(±DS) (kg)	8.9±0.5	9.2±0.9	9±1	9.1±0.2	9±0.8	9.3±0.9	9.1±1.1	9.4±1.5
(growth velocity)	(2.1±0.4)	(2.4±0.2)	(2±0.5)	(2.1±0.1)	(2.1±0.3)	(2.1±0.3)	(2.2±0.1)	(2±0.3)
Length(±DS) (cm)	72.4±1.3	74.5±1.2	72±1.6	74.5±0.9	71.9±1.6	75.1±0.9	70±2.1	73.4±0.7
(growth velocity)	(8.9±1)	(9.1±0.7)	(8.6±1.3)	(8.2±0.2)	(8.5±0.6)	(7.8±0.9)	(8.1±0.9)	(7.5±0.3)
Ferritin(±DS) (ng/ml)	17.2±0.9	18.9±0.6	20±0.4	19.7±0.6	19.2±0.9	19.6±1.1	20.1±0.9	22±1.2
TSI(±DS) (%)	16±1.2	16.5±0.9	18±0.9	19.2±0.5	20±1.4	21±0.6	23±1.4	24±2.2

Note: Hb $P<0.05$ a *vs* e, g; c *vs* e, g; $P>0.05$ a *vs* c; e *vs* g MCV $P<0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g Weight $P>0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g.
Hb $P<0.05$ b *vs* f, h; d *vs* f, h; $P>0.05$ b *vs* d; f *vs* h MCV $P<0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h Weight $P>0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h.
Length $P<0.05$ a *vs* g; c *vs* g; e *vs* g; $P>0.05$ a *vs* c, e; c *vs* e Ferritin $P<0.05$ a *vs* c, e, g; c *vs* e; e *vs* g; $P>0.05$ c *vs* g TSI $P<0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g.
Length $P<0.05$ b *vs* h; d *vs* h; f *vs* h $P>0.05$ b *vs* d, f; d *vs* f Ferritin $P<0.05$ b *vs* d, f, h; d *vs* h; f *vs* h; $P>0.05$ d *vs* f TSI $P<0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h.

Table 3 Haematological and anthropometric parameters in infants at 18 months according to iron supplementation

	BF and NIF foods		BF+IFF and foods		IFF and foods		BF+OIS	
	35 children		28 children		32 children		26 children	
	F(20) a	M(15) b	F (16) c	M(12) d	F(18) e	M(14) f	F(12) g	M(14) h
Hb(±DS) (g/dl)	11.6±0.5	11.7±0.5	12.1±0.4	12.2±0.5	12.2±0.5	12.4±0.5	12.6±0.4	12.5±0.6
MCV(±DS) (fl)	76.4±1.2	76.9±0.7	76.9±0.5	77.2±0.5	78.1±0.4	78.2±0.5	79.4±0.7	80.1±0.6
Weight(±DS) (kg)	10.7±1.2	11.8±1.2	10.5±0.9	12±0.9	11±0.7	12.5±0.7	11.9±1.8	12.6±0.9
(growth velocity)	(±)	(±)	(±)	(±)	(±)	(±)	(±)	(±)
Length(±DS) (cm)	78.9±0.9	81.1±2.1	78.2±1.2	80.2±2.2	78.1±1.6	80.1±2.3	77.1±0.6	78.1±1.2
(growth velocity)	(±)	(±)	(±)	(±)	(±)	(±)	(±)	(±)
Ferritin(±DS) (ng/ml)	17.9±1.9	18.1±1.6	20.2±0.7	20.1±0.6	20.6±0.9	21.7±0.8	20.7±1.2	22.1±2.1
TSI(±DS) (%)	16±1.2	17±1.9	18±2.1	19±2.3	20±0.7	21.2±0.9	22.2±1.2	20.9±1.7

Note: Hb $P<0.05$ a *vs* c, e, g; c *vs* g, e *vs* g; $P>0.05$ c *vs* e MCV $P<0.05$ a *vs* e, g; c *vs* e, g; e *vs* g; $P>0.05$ a *vs* c Weight $P>0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g.
Hb $P<0.05$ b *vs* d, f, h; $P>0.05$ d *vs* f, h MCV $P<0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h Weight $P>0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h.
Length $P<0.05$ a *vs* g; c *vs* g; e *vs* g; $P>0.05$ a *vs* c, e; c *vs* e Ferritin $P<0.05$ a *vs* c, e, g; $P>0.05$ c *vs* e, g; e *vs* g TSI $P<0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g.
Length $P<0.05$ b *vs* h; d *vs* h; f *vs* h $P>0.05$ b *vs* d, f; d *vs* f Ferritin $P<0.05$ b *vs* d, f, h; d *vs* f, h; $P>0.05$ f *vs* h TSI $P<0.05$ b *vs* d, f, h; d *vs* f, h; $P>0.05$ f *vs* h.

higher in BF, BF+IFF and IFF infants than in those receiving OIS.

Breast feeding children observed at 18 months of age also show significant lower haematological parameters than others. Weight is not significantly different among the groups while significant higher values of height are observed in BF, BF+IFF, IFF children than children with OIS.

Breast feeding and BF+IFF children aged 24 months also show significant lower haematological values than others but also significant lower weight than those who received IFF and OIS and significant higher height than other groups.

Discussion

In the last years, many studies have been performed to well document benefits and risks of indiscriminate IS.[6–11] Particularly it has been suggested that linear and weight growth might be impaired in iron sufficient infants that receive iron supplements.[6–11]

The evaluation of haematological and anthropometric parameters in our cohort of children followed since the sixth month of life during routine 24 month visits shows that with IS – both as IFF and foods and as OIS-haematological values are significantly higher than in infants that received exclusively BF and NIF foods.

On the contrary, linear growth of infants and children not receiving IS was significantly higher than other groups receiving IFF and foods or OIS. On the contrary, at 12 months children, that had not received IS, showed lower weight than other groups.

The effect of IS particularly in younger children living in countries with high prevalence of anaemia led to significant improvement of haematological parameters; except in cases where the anemia was due to different causes.

Table 4 Haematological and anthropometric parameters in infants at 24 months according to iron supplementation

	BF+NIF foods		BF+IFF and foods		IFF and foods		BF+OIS	
	35 children		28 children		32 children		26 children	
	F(20) a	M(15) b	F (16) c	M(12) d	F(18) e	M(14) f	F(12) g	M(14) h
Hb(±DS) (g/dl)	12.1±0.8	12.2±0.5	12.2±0.9	12.2±0.3	12.3±0.6	12.5±0.5	12.9±0.3	12.7±0.9
MCV(±DS) (fl)	78.1±0.9	77.4±1.2	77.9±0.8	78.1±0.6	80.5±2.1	82.1±1.2	83.6±2.1	83.2±1.9
Weight(±DS) (kg)	10.9±1.2	11.5±0.9	11.2±0.7	12.3±1.8	12.4±1.4	12.7±1.4	12.8±1.1	12.9±2.1
(growth velocity)	(±)	(±)	(±)	(±)	(±)	(±)	(±)	(±)
Length(±DS) (cm)	84.2±2.1	86.6±1.4	83.5±1.9	86.9±1.2	82.6±1.6	84.9±2.6	82.1±1.9	83.5±1.9
(growth velocity)	(±)	(±)	(±)	(±)	(±)	(±)	(±)	(±)
Ferritin(±DS) (ng/ml)	20±0.3	20±0.7	21±0.7	21±1.7	23±1.8	22±1.4	23±2.4	22±0.9
TSI(±DS) (%)	19±1.2	19±1.4	19±1.6	19.5±1.4	19.2±1.8	19.4±1.7	19.8±1.1	20.1±1.7

Note: Hb $P<0.05$ a *vs* g; c *vs* g, e *vs* g; $P>0.05$ a *vs* c, e; c *vs* e MCV $P<0.05$ a *vs* e, g; c *vs* e, g; e *vs* g; $P>0.05$ a *vs* c.
Hb $P<0.05$ b *vs* h; d *vs* h; $P>0.05$ b *vs* d, f; d *vs* f; f *vs* h MCV $P<0.05$ b *vs* f, h; d *vs* f, h; $P>0.05$ b *vs* d; f *vs* h
Weight $P<0.05$ a *vs* e, g; c *vs* e, g; $P>0.05$ a *vs* c; e *vs* g Lenght $P<0.05$ a *vs* e, g; c *vs* g; $P>0.05$ a *vs* c *vs* e *vs* g.
Weight $P<0.05$ b *vs* f, h; $P>0.05$ b *vs* d, d *vs* f, h; f *vs* h Lenght $P<0.05$ b *vs* f; h;d *vs* h; $P>0.05$ b *vs* d *vs* f *vs* h.
Ferritin $P<0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g TSI $P>0.05$ a *vs* c, e, g; c *vs* e, g; e *vs* g.
Ferritin $P<0.05$ b *vs* d, f, h; d *vs* f, h; $P>0.05$ f *vs* h TSI $P>0.05$ b *vs* d, f, h; d *vs* f, h; f *vs* h.

This consideration is very important because it is estimated that ID affects about 2 billion people worldwide.[2] Iron is essential for development of all tissues and in young children plays an important role since early months of life on neural myelination and on growth and immunologic processes.[8]

However, an excess iron leads to oxidative damage generating free radicals with alteration of cellular and enzymatic functions.[8] Adverse effects of IS in iron sufficient young children could be also explained by immature regulation of iron transporters in this age.[7] Furthermore, excess of metal could determine a reduction of absorption of other nutrients such as zinc, copper that might result in growth alterations.[7]

Our data are in agreement with results of a cooperative study performed on Sweden and Honduras infants that showed significantly lower gains in length in both groups with Hb levels ⩾110 g/l. The conclusion of the authors was that routine IS may benefit young children with low Hb but may present risks for those with normal Hb values.[9]

More recently, a study conducted on literature review on randomized placebo-controlled trials (RCTs) since 1980, targeting young children 0–59 months of age living in developing countries has examined OIS as prevention in comparison with placebo, identifying 26 RCTs. It appears that IS may be of limited or no benefit for growth in iron sufficient children, while a benefit could be found in children with ID.[8]

Conclusion

Recent advances in the understanding of proteins and peptides regulating iron absorption have enhanced our knowledge of iron metabolism in infants and young children. However, regulation of iron transporters such as DMT1, ferroportin, hepcidin is immature particularly in infants therefore iron supplements may have adverse effects in infants and children, especially in those who are iron replete.[7]

Moreover, there are possible metabolic interactions between iron and several other minerals. Interactions between iron, zinc, copper and vitamin A[8] should be studied using appropriate research techniques and clinical trials, to systematically evaluate the effects of IS on infants and children.

More studies on larger cohorts of infants and children are needed to better determine risks and benefits of IS and iron fortified foods. Adoption of a cautious approach based on iron status screening, also evaluating the impact on the possible increase in infectious disease is recommended.

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