

ORIGINAL ARTICLE

Milk versus medicine for the treatment of iron deficiency anaemia in hospitalised infants

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Additional data are available on the ADC website (<http://www.archdischild.com/supplemental>)

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Aims: To compare iron fortified follow-on milk (iron follow-on), iron fortified partially modified cows' milk (iron milk), and iron medicine for the treatment of iron deficiency anaemia (IDA) in hospitalised infants.

Methods: In a randomised controlled trial, infants aged 9–23 months with IDA and who were hospitalised with an acute illness received iron follow-on (12 mg/l ferrous iron), iron milk (12.9 mg/l ferrous iron), or iron medicine (ferrous gluconate at 3 mg/kg of elemental iron once daily). All interventions were given for three months. Changes in measures of iron status three months after hospital discharge were determined.

Results: A total of 234 infants were randomised. Iron status was measured at follow up in 59 (70%) iron medicine, 49 (66%) iron follow-on, and 54 (70%) iron milk treated infants. There was a significant (mean, 95% CI) increase in haemoglobin (15 g/l, 13 to 16) and iron saturation (9%, 8 to 10) and decrease in ferritin (−53 µg/l, −74 to −31) in all three groups. Mean cell volume increased in iron follow-on (2 fl, 1 to 3) and iron milk (1 fl, 0.1 to 3) treated infants, but not in the iron medicine group (1 fl, −1 to 2). The proportion with IDA decreased in all three groups: iron medicine 93% to 7%, iron follow-on 83% to 8%, and iron milk 96% to 30%. Adverse effects, primarily gastrointestinal, occurred in 23% of the iron medicine, 14% of the iron follow-on, and 13% of the iron milk group.

Conclusions: Iron fortified follow-on milk, iron fortified partially modified cows' milk, and iron medicine all effectively treat IDA in infancy.

The treatment of iron deficiency anaemia (IDA) in infants and toddlers remains difficult. The current standard is iron medicine administered orally. While on an individual basis this can be effective, it is less than ideal therapy. Although efficacious in supervised trials, it has proven less effective in practice because of poor palatability, adverse gastrointestinal side effects, and non-compliance.^{1–4}

Alternatives therapies also have limitations. Intramuscular iron given early in infancy was more efficacious than oral iron supplements in a number of studies performed in the 1950s and 1960s.^{5,6} However, the potential for anaphylaxis and hypersensitivity reactions, plus the association with reduced resistance to bacterial infections, limit its use to refractory IDA.^{3,7–9}

Iron fortification of infant formulas has been successful in preventing IDA in a number of studies, but its treatment role has been less completely examined.¹⁰ Studies from Brazil and Argentina of iron deficient infants and young children have shown that the use of iron fortified whole milk is associated with correction of iron deficiency (ID) and IDA.^{11,12} The iron formulations and concentrations used, an iron amino acid chelate providing 3 mg iron/l in one, and microencapsulated ferrous sulphate providing 15 mg iron/l in the other, were different from the 12 mg/l used in standard infant or follow-on milk formulas.^{10–12} No studies of the use of milk products, containing standard concentrations of iron, to treat IDA have been reported.

The objective of this study was to determine if iron fortified follow-on milk was as effective as oral iron medicine in the treatment of IDA. We also determined if partially modified

iron fortified cows' milk was as effective as either of the other two interventions.

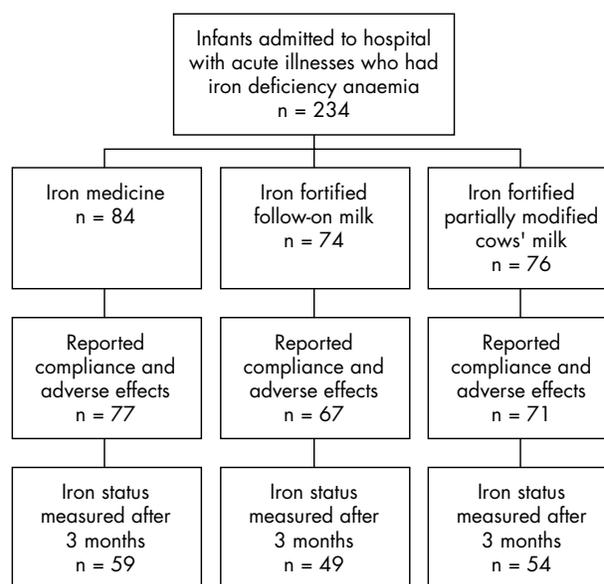


Figure 1 Randomisation of infants to the three interventions for iron deficiency anaemia and completion of study by those randomised.

METHODS

Participants

Infants were eligible if aged 9–23 months, resident in Auckland, New Zealand and presenting to the Starship Children's Hospital with an acute illness during 1997–99. Following informed consent, iron studies were performed. Infants were excluded if they had severe IDA (haemoglobin <70 g/l), another known cause for their anaemia, or a chronic illness likely to impair response to iron. Ethical approval was obtained from the Regional Health Authority.

Randomisation

Those infants with IDA were randomised to one of the three interventions using a sequential list generated by a biostatistician independent of the research team. A person (NT) not involved in recruitment performed intervention group assignment. The investigators were blinded with respect to the intervention. Participants were blinded with respect to either milk intervention. We did not believe it ethical to randomise infants with IDA to a placebo group.

Intervention

The three interventions, each provided without charge for three months, were: (1) oral iron elixir (iron medicine) at 3 mg/kg once per day of elemental iron as ferrous gluconate;

(2) iron fortified follow-on infant milk (iron follow-on) containing 12.0 mg/l iron as ferrous casienate, and vitamin C 124–195 mg/l; and (3) iron fortified partially modified cows' milk (iron milk) containing 12.9 mg/l iron as ferrous sulphate, and vitamin C 124–195 mg/l.

Both milk interventions were provided as powder in coded single serve sachets. Each sachet reconstituted to 250 ml. Mothers were provided with instructions on milk preparation and advised to use the intervention milk instead of any other milk or infant formula they would otherwise have given the infant (see table A for nutritional composition of the milk interventions; available on the ADC website: <http://www.archdischild.com/supplemental>). All those enrolled received dietary advice on weaning foods that provide adequate dietary iron. Infants with ID at follow up were prescribed oral iron elixir for three months.

Determination of iron status

Iron status was determined at enrolment and on completion of the trial three months later. ID was defined in a manner similar to that used for the United States National Health and Nutrition Examination Surveys with the exception that the red cell distribution width (RDW) rather than the erythrocyte protoporphyrin was used as the measure of erythrocyte iron.¹³ RDW was used in preference to mean cell volume (MCV) as

Table 1 Comparison of infants and maternal characteristics of the three intervention groups at enrolment: oral ferrous gluconate (iron medicine), iron fortified follow on milk (iron follow-on), and iron fortified partially modified cows' milk (iron milk)

Variable	Intervention group		
	Iron medicine n ₁ = 84	Iron follow-on n ₂ = 74	Iron milk n ₃ = 76
Infant characteristics			
Age (months)	14.6 (9.4, 23.3)	14.2 (8.9, 20.8)	12.8 (9.2, 22.8)
Birth weight (kg)*	3.4 (1.8, 4.3)	3.4 (2.3, 4.3)	3.2 (1.8, 4.5)
Gestation in weeks†	40 (35, 42)	40 (34, 42)	40 (34, 42)
Male gender	53 (63)	42 (57)	41 (54)
Ethnicity			
European/other	32 (38)	16 (21)	15 (20)
Maori	13 (16)	19 (26)	16 (21)
Pacific	39 (46)	39 (53)	45 (59)
Diagnosis			
Pneumonia	22 (26)	20 (27)	31 (41)
Bronchiolitis	11 (13)	13 (18)	11 (14)
Acute febrile illness	9 (11)	13 (18)	6 (8)
Surgical/orthopaedic	13 (15)	8 (10)	8 (10)
Gastroenteritis	6 (7)	3 (4)	6 (8)
Asthma	4 (5)	3 (4)	3 (4)
Upper respiratory infection	3 (4)	3 (4)	2 (3)
Other	16 (19)	11 (15)	9 (12)
Infant feeding practices			
Breast fed at birth‡	67 (80)	67 (92)	64 (84)
Breast fed at enrolment§	27 (32)	19 (26)	20 (27)
Has tea to drink	9 (11)	22 (30)	17 (22)
Age started cows' milk¶	7 (0, 18)	7 (0, 14)	9 (0, 17)
Age started solids**	5 (3, 9)	5 (3, 9)	5 (3, 10)
Maternal and household characteristics			
Maternal age (years)††	31 (20, 39)	28 (20, 38)	29 (19, 38)
Mother restricted meat intake‡‡	15 (18)	12 (16)	20 (27)
Annual household income ≤ \$30,000§§	39 (54)	36 (61)	47 (76)
Proportion of weekly income spent on food¶¶	0.23 (0.11, 0.63)	0.23 (0.10, 0.83)	0.28 (0.07, 0.88)
Number of people in household <16 years of age***	2 (1, 5)	3 (1, 6)	2 (1, 5)

Results expressed as n (%) or median (5th, 95th centiles).

*n₁ = 73, n₂ = 62, n₃ = 70; †n₁ = 72, n₂ = 61, n₃ = 69; ‡n₂ = 73; §n₃ = 75; ¶n₂ = 72, n₃ = 75; **n₁ = 83, n₂ = 73;

††n₁ = 82, n₃ = 75; ‡‡n₁ = 83, n₂ = 73, n₃ = 75; §§n₁ = 72, n₂ = 59, n₃ = 62; ¶¶n₁ = 69, n₂ = 57, n₃ = 59;

***n₁ = 83, n₂ = 70, n₃ = 74.

Table 2 Effect of increased C reactive protein on measures of iron status at enrolment

Measure of iron status at enrolment	C reactive protein (mean, 95% CI)		p value‡
	Normal (n = 35)	Increased† (n = 93)	
Haemoglobin (g/l)	104 (102 to 105)	101 (99 to 103)	0.03
Ferritin* (µg/l)	18 (12 to 28)	47 (39 to 57)	<0.001
Iron saturation* (%)	6.6 (5.9 to 7.5)	4.3 (3.9 to 4.8)	<0.001
Red cell distribution width* (%)	16.0 (15.6 to 16.5)	16.1 (15.8 to 16.4)	0.86
Mean cell volume (fl)	70 (68 to 72)	72 (70 to 73)	0.33

*For ferritin, iron saturation, and red cell distribution width, these are geometric means and confidence intervals.

†C reactive protein >6 mg/l.

‡† test.

the measure of erythrocyte iron because of the high prevalence of α -thalassaemia trait in Polynesian New Zealanders.¹⁴

ID was defined as abnormal values for two of the following: serum ferritin concentration (<10 µg/l), serum iron saturation (<10%), and RDW (>14.5%).^{13, 15} IDA was defined as ID plus anaemia (haemoglobin <110 g/l). C reactive protein was measured to enable adjustment for the effects of acute inflammation on measures of iron status.¹⁶ An increased C reactive protein was defined as greater than 6 mg/l.

Statistical analysis

The reported efficacy of oral iron medicine for treating IDA, where direct observation of drug administration is not used, ranges from 12% to 61%.¹⁻³ Based on an estimation that the current standard of practice (iron as an oral elixir) corrected IDA in 50% of cases, and estimating that for either of the milk interventions to be a significant improvement would require it to correct IDA in 75% of cases, we required 65 subjects in each of the three intervention groups ($\alpha = 0.95$, $\beta = 0.2$).¹⁷ A total sample size of 255 subjects (85 in each intervention group) was therefore considered necessary to allow for a 25% dropout rate.

A face to face interview was completed at enrolment and follow up. At enrolment data were collected on the infant and household demographics, household socioeconomics, pregnancy history, mother's iron intake during the pregnancy, the infant's feeding history, and diet at enrolment. At the three month follow up interview, data were collected on compliance with the intervention and on any illnesses that the infant had experienced since enrolment.

Data were double entered and analysed using Epi-info version 6, SAS-PC version 8.2 and confidence interval analysis software.¹⁷⁻¹⁹ Enrolment and follow up measures of iron status were compared and 95% confidence limits estimated for the differences. The effect of the interventions on all measures of iron status at follow up was compared (haemoglobin, ferritin, iron saturation, red cell distribution width, mean cell volume, ID, IDA). Multiple regression

analyses were used to adjust these comparisons for enrolment measures of iron status, C reactive protein, and variables known to be associated with iron deficiency anaemia in this population. These variables were Pacific ethnicity, having a diagnosis of pneumonia, currently drinking breast milk, maternal restriction of meat intake during pregnancy, and living in a household with more than three children.²⁰ Non-normally distributed dependent variables (ferritin, iron saturation, RDW, and C reactive protein) were log transformed. With the exception of C reactive protein the transformed variables were normally distributed.

RESULTS

Two hundred and thirty four infants were randomised: 84 (35%) to iron medicine, 74 (32%) to iron follow-on, and 76 (33%) to iron milk (fig 1). Three month follow up blood samples were obtained from 59 (70%) of the iron medicine, 49 (66%) of the iron follow-on, and 54 (71%) of the iron milk group. There were no differences in any of the enrolment measures of iron status in comparisons between the 162 (69%) infants who completed follow up and the 72 (31%) that did not (data not shown).

Eighteen infants who did not meet the criteria for IDA were inadvertently enrolled. Fourteen of these infants completed the study, four of whom were randomised to iron medicine, eight to iron follow-on, and two to iron milk. Eleven of these 14 infants had ID, but haemoglobin concentrations that were 110 g/l in seven, 111 g/l in three, and 113 g/l in one. Three infants, all with anaemia, did not have ID. All three had abnormal values for one of the three measures of iron status.

Infant characteristics and feeding practices were similar in the three intervention groups except for the proportion who drank tea (table 1). Maternal and household characteristics did not vary except for the proportion of households with an annual income \leq \$30,000.

The effect of an increased C reactive protein on measures of iron status at enrolment is shown in table 2. Red cell distribution width and mean cell volume did not differ with increase of C reactive protein. Ferritin was higher

Table 3 Enrolment and follow up iron status measures for the 162 infants who completed the study

Measure of iron status	Enrolment Median (5th, 95th centile)	Follow up Median (5th, 95th centile)	Comparison Mean difference (95% CI)*
Haemoglobin (g/l)	104 (84, 110)	117 (99, 131)	15 (13 to 16)
Ferritin (µg/l)	42 (6, 216)	19 (5, 78)†	-53 (-74 to -31)
Iron saturation (%)	5.0 (2.0, 9.0)	14.0 (4.0, 29.5)‡	8.8 (7.5 to 10.1)
Red cell distribution width (%)	16 (15, 19)	16 (14, 19)§	0.10 (-1.8 to 0.38)
Mean cell volume (fl)	72 (60, 81)	73 (62, 80)	1.3 (0.6 to 2.0)

*For ferritin, iron saturation, and red cell distribution width, these are geometric means and confidence intervals.

†n = 155; ‡n = 160; §n = 151.

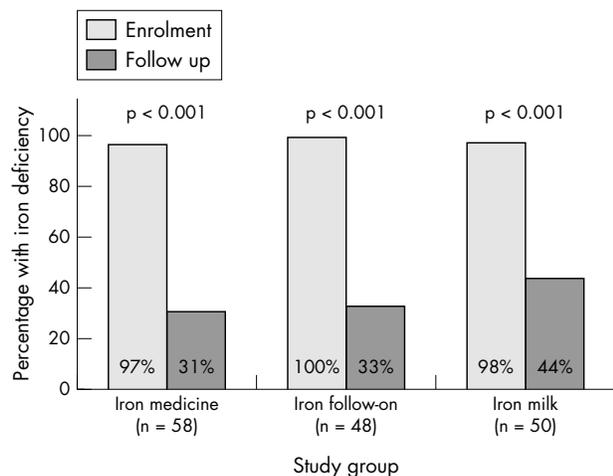


Figure 2 Percentage of infants with iron deficiency at enrolment and completion.

($p < 0.001$), and haemoglobin ($p = 0.03$) and iron saturation ($p < 0.001$) were lower in those with an increased C reactive protein.

The enrolment and follow up iron status measures for the infants who completed the study are shown in table 3. Haemoglobin, iron saturation, and mean cell volume increased and ferritin decreased. When analysed by each intervention (mean, 95% CI), haemoglobin (iron medicine 15 g/l, 12 to 18; iron follow-on 16 g/l, 13 to 19; iron milk 13 g/l, 10 to 16) and iron saturation (iron medicine 10%, 7 to 12; iron follow-on 9%, 7 to 11; iron milk 8%, 6 to 9) increased in all three. Mean cell volume increased in iron follow-on (2 fl, 1 to 3) and iron milk groups (1 fl, 0.1 to 3) but not the iron medicine group (1 fl, -1 to 2). Ferritin decreased in all three groups: iron medicine (-39 $\mu\text{g/l}$, -60 to -18), iron follow-on (-71 $\mu\text{g/l}$, -125 to -14), and iron milk (-51 $\mu\text{g/l}$, -82 to -18).

The effects of the three interventions on each of the follow up measures of iron status were compared (table 4). Each of these comparisons was adjusted for the enrolment measure of iron status and then also for C reactive protein and the variables previously shown to be associated with iron deficiency anaemia in this population.²⁰ In the multivariate comparison with iron medicine, RDW was significantly greater in the iron milk group ($p = 0.03$).

The analyses shown in tables 3 and 4 were repeated with exclusion of the 14 ineligible infants. The increases in haemoglobin (15 g/l, 13 to 17), iron saturation (9%, 8 to 10), and mean cell volume (1.5 fl, 0.8 to 2.2), and decrease in

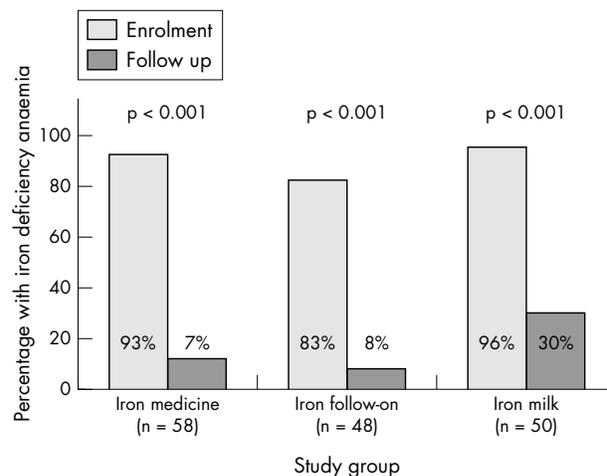


Figure 3 Percentage of infants with iron deficiency anaemia at enrolment and completion.

ferritin (-41 $\mu\text{g/l}$, -58 to -24) were similar. RDW in the iron milk group remained significantly greater in the multivariate comparison with the iron medicine group ($p = 0.03$).

The change in proportion of infants with ID and IDA in each of the three groups is shown in figs 2 and 3. Significant reductions in the proportion with ID and with IDA occurred in all three groups (all $p < 0.001$). The change in proportion with ID did not differ for iron follow-on (RR = 1.04, 0.91 to 1.20) or iron milk (RR = 1.11, 0.97 to 1.27) versus iron medicine. The change in proportion with IDA did not differ for iron follow-on (RR = 0.87, 0.74 to 1.04) but did for iron milk (RR = 1.19, 1.03 to 1.38) versus iron medicine.

Compliance was reported for 77 (92%) of the iron medicine, 67 (91%) of the iron follow-on, and 71 (93%) of the iron milk group. The intervention was given each day to 65 (84%) of the iron medicine, 61 (91%) of the iron follow-on, and 57 (80%) of the iron milk group ($p = 0.14$). The intervention was difficult to give to 24 (31%) of the iron medicine, 14 (21%) of the iron follow-on, and 19 (27%) of the iron milk group ($p = 0.38$).

Data on adverse effects were available for 76 (91%) of the iron medicine, 66 (89%) of the iron follow-on, and 68 (90%) of the iron milk group. Adverse effects were reported by 19 (25%) of the iron medicine, 10 (15%) of the iron follow-on, and 10 (15%) of the iron milk group ($p = 0.20$). Adverse effects in the iron medicine group were constipation (11), stained teeth (4), unpleasant taste (2), vomiting (1), and diarrhoea (1). In the iron follow-on group they were unpleasant taste (2), vomiting (1), diarrhoea (3), constipation

Table 4 Comparison of follow up measures of iron status in the three intervention groups

Follow up measure	Intervention group Median (5 th , 95 th centile)			Iron follow-on versus iron medicine (p value)		Iron milk versus iron medicine (p value)	
	Iron medicine (n ₁ = 59)	Iron follow-on (n ₂ = 49)	Iron milk (n ₃ = 54)	Bivariate*	Multivariate†	Bivariate*	Multivariate†
Haemoglobin (g/l)	118 (99, 134)	120 (104, 132)	115 (94, 127)	0.45	0.98	0.26	0.52
Ferritin‡§ (µg/l)	22 (4, 92)	17 (7, 65)	20 (4, 56)	0.14	0.42	0.21	0.94
Iron saturation¶ (%)	14 (3, 34)	15 (5, 29)	12 (5, 24)	0.66	0.47	0.35	0.44
Red cell distribution width‡** (%)	16 (14, 18)	16 (14, 20)	17 (14, 18)	0.25	0.18	0.22	0.03
Mean cell volume (fl)	74 (61, 82)	73 (66, 79)	73 (60, 80)	0.17	0.23	0.90	0.80

*Adjusted for enrolment iron measure.

†Adjusted for enrolment iron measure, initial C reactive protein, Pacific ethnicity, having a diagnosis of pneumonia, currently drinking breast milk, maternal restriction of meat intake during pregnancy, and living in a household with more than three children.

‡Log_e transformed as dependent variable for regression analysis.

§n₁ = 57, n₂ = 48, n₃ = 50; ¶n₂ = 48, n₃ = 53; **n₁ = 56, n₂ = 45, n₃ = 50.

What is already known on this topic

- The current standard treatment for iron deficiency anaemia in infants is iron medicine administered orally
- Iron fortified infant formula prevents iron deficiency anaemia but it is not known whether it can also be used to treat iron deficiency anaemia

(1), and other (3); and in the iron milk group unpleasant taste (4), vomiting (2), diarrhoea (2), and other (2).

DISCUSSION

Iron fortified follow-on milk, iron fortified partially modified cows' milk, and iron medicine all effectively treated IDA in this sample of hospitalised infants. Iron milk was not as effective as iron medicine. The frequency of adverse effects was similar in all three. Thus iron fortified milk formula appears to be an acceptable alternative to iron medicine for the treatment of IDA.

A limitation of this study was that the majority of subjects were hospitalised with acute infection. Determination of iron status when acute illness is present is difficult. However, in the absence of screening, this is frequently the situation in which IDA is diagnosed. Recent infections cause a decrease in serum haemoglobin concentration and iron saturation and an increase in ferritin concentration.²¹ Such changes make it potentially difficult to interpret the response to supplemental iron therapy.

We were able to show that not all measures of iron status are affected by the acute inflammatory response. Neither of the two red cell measures, RDW and mean cell volume, varied with increase of C reactive protein. Thus these parameters, both available from a full blood count, are useful diagnostic tests for iron deficiency in infants hospitalised with acute illnesses. Whether, in addition, measurement of iron saturation and ferritin provides useful information in diagnosing iron deficiency in this setting is debatable.

After completion of the intervention haemoglobin and mean cell volume increased but RDW did not. As the RDW measures variability in red cell size, it is to be expected that this will remain abnormal for several months after starting treatment of ID. Treatment will maintain a dual population of smaller (older) red cells made when the child was iron deficient and larger (younger) red cells made after iron supplementation was commenced. Therefore, although in ID the increase in RDW occurs earlier than the changes in haemoglobin or mean cell volume, these later two parameters appear more useful for determining if there has been a response to iron therapy.²²

Some infants were included into the intervention groups whose iron status, although abnormal, did not meet eligibility criteria. We did not become aware of this until follow up was completed. It was considered preferable that these infants be included in the analyses. Exclusion of these 14 from the analysis did not change the results significantly.

We did not attempt to blind the comparison of medicine to milk. It would have been unethical to deliver a placebo milk, as a principal nutrient source, which contained no iron.

The iron follow-on and iron milk interventions both contained many micronutrients in addition to iron. Although not measured in this study, children with IDA are also at increased risk of other micronutrient deficiencies.^{23 24} Hence, an intervention that can deliver many different micronutrients rather than a single micronutrient is a superior health intervention.

What this study adds

- In children aged 9–24 months with iron deficiency anaemia, iron fortified follow-on milk, iron fortified partially modified cows' milk, and iron medicine are all effective treatments
- Iron fortified milk formula is an acceptable alternative to iron medicine for the treatment of iron deficiency anaemia

A significant proportion of infants failed to respond to each of the interventions. The reasons for this are unknown but are a feature of other oral interventional studies.^{1 25} This non-response could be due to poor compliance, inadequate treatment, other dietary habits, or differences between individuals in absorption, other micronutrient status, or other characteristics that affect iron utilisation.²⁶ This implies the need for follow up of iron deficient infants after treatment and for any intervention to last longer than three months for some infants.

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Competing interests: none

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IMAGES IN PAEDIATRICS.....

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Intra-articular calcifications in a child with juvenile rheumatoid arthritis



An 8 year old girl with pauci-articular juvenile rheumatoid arthritis associated with positive antinuclear antibodies testing, arrived in the emergency department with severe right knee pain after a fall on both knees four days earlier. She had developed bilateral bruising with swelling and limited range of motion of the right knee, with no fever. She was found on plain x ray examination to have calcifications in joints injected previously with steroids. The girl was treated with a non-steroidal anti-inflammatory drug and the pain resolved after few days.

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