

Prevention of iron-deficiency anemia: Comparison of high- and low-iron formulas in term healthy infants after six months of life
[Original Articles]

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Abstract

Objectives: For bottle-fed babies or nursing infants who receive milk supplements, the American Academy of Pediatrics recommends the use of iron-fortified infant formula. Because these recommendations have not been universally adopted, the hematologic effects of currently available low-iron formulas need to be determined.

Study design: Healthy Chilean 6-month-old infants (without iron-deficiency anemia, born at term weighing \geq to 3.0 kg) who were totally or partially weaned from the breast were randomly allocated in a double-blind fashion to receive high-iron (n = 430) or low-iron formula (n = 405), containing an average of 12.7 mg/L or 2.3 mg/L, respectively, of elemental iron as ferrous sulfate. Iron status was determined at 12 months.

Results: The prevalence of iron-deficiency anemia was not different in the high- and low-iron groups (2.8% versus 3.8%, $p = 0.35$). Nevertheless, infants receiving high-iron formula had somewhat higher levels of hemoglobin and serum ferritin, greater mean cell volumes, and lower erythrocyte protoporphyrin levels ($p < 0.005$).

Conclusions: Although high-iron formulas are more efficacious in improving iron status, currently available low-iron formulas may prevent iron-deficiency anemia in selected healthy, term infant populations with otherwise poor sources of dietary iron after 6 months of life. Formulas with relatively small amounts of iron appear to prevent iron-deficiency anemia. We speculate that the optimal level of iron fortification likely lies somewhere between the current levels in high- and low-iron formulas. (J Pediatr 1998;132:635-40.)

([Table IV](#)) Infancy is a period of particularly high risk for the development of iron deficiency. Neonatal stores are markedly reduced by 4 to 6 months in the term infant and much earlier in the low-birth weight neonate. After this age, the infant is dependent on dietary sources to maintain adequate iron status. The relatively low iron content (0.8 - 1.0 mg/L) and bioavailability of iron in whole cow's milk (4% absorption) render it a poor source of iron during infancy. [\[1\]](#) Modified infant formulas, containing between 1.5 and 14 mg/L of elemental iron plus ascorbic acid to enhance iron absorption, have therefore been used to prevent iron deficiency. Rios et al. [\[2\]](#) showed that the absorption of iron from proprietary formulas containing 12 mg/L or more of elemental iron as ferrous sulfate averaged 4.2%. The amount absorbed was considered adequate because an infant consuming 850 ml would absorb close to the daily requirement of 0.5 - 0.9 mg of elemental iron. The formulas fortified with 12 mg/L of elemental iron are effective in preventing iron-deficiency anemia in the United States. [\[3-5\]](#) The American Academy of Pediatrics recommended the use of formula fortified with 12 mg/L of elemental iron during the first year of life. [\[6\]](#) Few countries other

than the United States have endorsed these guidelines. Use of unfortified formulas, containing a minimum of 1.5 mg/L of elemental iron, remains common in many countries, both industrialized and developing. Empirical evidence exists that lower-iron formulas are meeting infant iron needs better than predicted from the available absorption data. In 1980, Picciano and Deering [7] compared an iron-fortified formula (14 mg/quart) with a low-iron formula (1.4 mg/quart) during the first 4 months of life and found no difference in hemoglobin level or transferrin saturation at 9 or 12 months. Haschke et al. [8] compared infants fed formulas with either 3 or 6 mg/L of iron and found no differences in iron status of infants aged 9 months. Lonnerdal and Hernell [9] showed that formulas with 4 or 7 mg of iron/L were equally effective in maintaining good iron status during the first 6 months of life.

Table IV. No caption available.

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These studies suggest that low-iron formulas do not necessarily lead to poor iron status, even though the dietary intake of iron is theoretically insufficient to meet requirements. One possible explanation for this apparent contradiction is that the infants had adequate intake of iron from other sources. The studies were conducted in industrialized countries involving relatively affluent families who had ready access to other foods that were iron-fortified or contained highly bioavailable iron, such as infant cereals or meat. [10] For a more accurate evaluation of the effects of low-iron formulas per se on iron nutrition, research is needed in countries such as Chile, where infant health is generally excellent but iron-deficiency anemia is common because iron sources are limited. A lack of iron-fortified infant products or other effective iron supplementation programs has meant that 27% to 35% of Chilean infants fed powdered cow's milk develop iron-deficiency anemia at ages 9 to 18 months, and biochemical evidence of iron deficiency is present in 43% to 65%. [11,12] As part of a larger study on iron-deficiency anemia and behavior, we had the opportunity to compare the iron status of healthy Chilean infants who received either a high-iron (fortified) or low-iron (unfortified) formula.

Methods

Setting

Chile is a South American democracy with a highly literate population and a comprehensive health care system. According to Chilean custom, almost all babies are breast fed in the early months and about 50% continue to breast feed up to 6 months of age. However, unmodified powdered cow's milk is distributed free of charge at all health maintenance visits as part of a long-standing, highly effective program to prevent malnutrition. Routine pediatric care and infant

feeding practices in Chile during this study did not include iron supplementation, although a national program of iron fortification of milk for infants was scheduled to start in 1997. Solid foods (fruit and cereal) usually are introduced at 4 months of age, with meat and vegetables added at 6 months, and legumes and eggs at 9 months. This diet provides approximately 5 mg of iron, mostly of vegetable origin with poor bioavailability. [13] Hookworm and hemoglobinopathic conditions are virtually nonexistent. The current study was conducted in four contiguous urban communities on the southeastern outskirts of Santiago. The communities, with running water, sewage, and electricity, are located at an elevation of 600 m and inhabited by primarily lower middle-class residents, generally homogeneous in ethnic origin.

Procedures Used to Identify Study Participants

Infants receiving routine pediatric care in the four community clinics were evaluated at the 4-month visit. The following entrance criteria were used to enroll healthy infants into the trial: birth weight \geq to 3.0 kg, single birth, no major congenital anomalies, no major birth or neonatal complications, no emergency cesarean section, no jaundice requiring phototherapy, no hospitalization for longer than 5 days, no chronic illness, and no iron therapy. Other entrance criteria were specific to successful completion of the study: residence within the identified neighborhoods; a stable, literate care giver who was available to accompany the child for project appointments; no other infant younger than 12 months in the household; and infant not in day care. The final entrance criterion was that the child had already started to receive some bottle feedings by 6 months of age. However, all project personnel encouraged mothers to continue breast feeding.

The study was explained to parents of qualifying infants, and those who were interested received 2 to 3 home visits by a study dietitian. The dietitians confirmed the entrance criteria, explained the study again to the family, and obtained signed informed consent. The research protocol was approved by the Institutional Review Boards of the University of Michigan Medical Center, Ann Arbor, Michigan, the Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, and the National Institutes of Health Office of Protection from Research Risks.

Parents of 94.3% of the infants who met the entrance criteria agreed to participate ($n = 1179$). At ages between 5 and 6 months, the infants underwent finger stick hemoglobin determinations (HemoCue, Leo Diagnostics, Helsingborg, Sweden). If the HemoCue value was < 103 gm/L, a venipuncture was immediately performed. Infants with hemoglobin levels \leq to 100 gm/L confirmed on the venous sample and 2 of 3 iron measures in the deficient range (mean cell volume < 70 fL, erythrocyte protoporphyrin > 100 micro g/dL red blood cells or serum ferritin < 12 micro g/L) were treated with oral iron and did not enter the clinical trial. Thirty infants were disqualified for this reason, along with 29 infants with higher hemoglobin levels for comparison. Both the anemic 6-

month-old infants and control subjects were invited to participate in a different study. [14] Complete iron measures were not performed on all infants screened by HemoCue, because the distress of venipuncture and cost of iron studies did not seem justified, given that iron deficiency is uncommon at this age. The cut-offs for iron status measures at each age were approximately 2 SD below the mean. [15] At all ages, blood sampling was postponed if an infant was sick or had been febrile in the preceding 2 weeks.

One thousand one hundred twenty healthy infants entered the trial. Subsequent attrition, equally distributed between high- and low-iron groups, was 25.4%, mostly the result of household moves or protocol noncompliance. Thus data for 835 infants who completed the trial were available to assess the effects of low- and high-iron formulas.

Procedures for the Clinical Trial

Between July, 1991, and August, 1994, the infants were randomly assigned at 6 months of age to receive high-iron formula (average 12.7 mg/L) or low-iron formula (average 2.3 mg/L, range 1.6-2.4 mg/L; content given by Abbott-Ross Laboratories and confirmed in our laboratory). High- and low-iron formulas were distributed, in powdered form, in cans with identical labels except for different milk numbers (with two numbers corresponding to high-iron formula, and another two corresponding to low-iron formula). The milk numbers were placed on the cans at INTA by laboratory personnel who had no contact either with study families or with field workers. Only the project coordinators had access to the code indicating which numbers corresponded with which kind of formula. At the clinics, study personnel gave participating infants the next available milk number on a list of predetermined, randomly generated milk numbers. Thus the study was double-blind, with families and project personnel unaware of whether the infant received high- or low-iron formula.

Project personnel visited the infants' homes weekly to record respiratory and gastrointestinal symptoms and collect parents' daily records of feeding (number of nursings at the breast; measures of powdered formula used per day, where each measure corresponded to 60 ml of prepared formula; amount left over after each feeding). All babies received regular pediatric check-ups and growth measurements at monthly clinic appointments until 12 months of age. Formula consumption also was verified by the number of cans given by the clinic nurse at each visit. At 12 months, infants were transported to INTA for a venipuncture blood specimen (7 - 10 ml) for determination of hemoglobin, hematocrit, mean cell volume (using Coulter Model ZBI, Hialeah, Fla.), serum ferritin, [16] and erythrocyte protoporphyrin (Hematofluorometer, Helena Laboratories, Beaumont, Texas) values. Nonanemic infants in the low-iron group continued to be followed up, with these same measures repeated at 18 months. Iron-deficiency anemia at 12 and 18 months was defined as a hemoglobin level 110 gm/L or lower and abnormal values on at least 2 of 3 measures of iron status (serum ferritin < 12 micro g/L, erythrocyte protoporphyrin > 100 micro g/L red blood cells, or mean

cell volume < 70 fL), or increase in hemoglobin \geq to 10 gm/L after iron therapy. Infants with iron-deficiency anemia at 12 or 18 months were treated with therapeutic doses of oral iron and followed up separately. Study participants received formula, pediatric care, laboratory evaluations, and transportation to and from INTA free of charge.

To help interpret the results, the bioavailability of the iron in the low-iron preparation was assessed using the double-isotope iron absorption method of Eakins-Brown. [17] In brief, 15 multiparous women, who were using contraception and tested negative for pregnancy, fasted overnight and then were given 250 ml of the low-iron formula tagged with 59 ferric chloride, 3 micro Ci per dose. No food or drink was permitted in the following 4 hours. A reference dose of 55 ferric chloride (1 micro Ci per dose) in 3 mg of elemental iron as ferrous ascorbate was given the next day under the same conditions. Circulating radioactivity as incorporation of radioactive iron in hemoglobin was measured 15 days later using a liquid scintillation counter with a 3% counting error. For comparison, formulas with high iron content also were measured in our laboratory.

Data Analysis

All analyses were performed using standard statistical packages (SPSS version 4; Statistical Package for the Social Sciences, SPSS Inc., Chicago, Ill.). Differences between the high- and low-iron formula groups were evaluated by ANOVA for continuous variables and the chi squared test for categorical variables. An alpha-level of 0.05 was used in two-tailed tests of statistical significance.

Results

Eight hundred thirty-five infants completed the trial, randomly assigned to receive low-iron formula (n = 405) or high-iron formula (n = 430). The two groups were similar with respect to demographic characteristics, infant growth, formula consumption, and most measures of breast feeding (Table I). The infants in the two groups were well nourished at both 6 and 12 months, as indicated by growth parameters at the 50th percentile by U.S. standards. Infants in the low-iron group were breast fed an average of 21 days longer than those in the high-iron group, but there were no statistically significant differences in the duration of receiving breast milk as sole source of milk or the proportion at or above the median for age either at introduction of bottle feedings or at complete weaning from the breast. The average intake of formula between 6 and 12 months of age was similar in low- and high-iron groups, about 620 +/- 181 ml/day.

Table I. Background factors, growth, and feeding

[\[Help with image viewing\]](#)

The effects of the two formulas on infant iron status at 12 months are shown in [Table II](#). Low-iron formula was surprisingly effective in preventing iron-deficiency anemia. At 12 months of age, only 3.8% of the low-iron group had iron-deficiency anemia, compared with 2.8% of the high-iron group ($p = 0.35$). Differences in mean values of iron status measures were minor from a clinical perspective, though all comparisons were statistically significant because of the relatively large sample size. However, a substantially higher proportion of nonanemic infants in the low-iron group had 2 of 3 iron measures in the deficient range (35% versus 17% in the high-iron group, $p < 0.001$).

Table II. Hematologic status at 12 months

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To assess the relationship between the quantity of formula consumed and infant iron status, we identified infants who were in the lower 20th percentile for average total intake per day, arbitrarily considering this level of consumption to be "insufficient" for optimal benefits of iron fortification: less than 479 ml/day in the high-iron formula and less than 490 ml/day in the low-iron preparation. In the high-iron formula group, the prevalence of iron-deficiency anemia was 5.8% among infants with insufficient intake, compared with 1.0% among those with sufficient consumption ($p < 0.001$), and the mean hemoglobin level was lower (123.2 +/- 9.5 gm/L versus 125.6 +/- 7.9 gm/L, $p < 0.01$). In the low-iron formula group, there was no association between insufficient intake and poorer iron status.

Iron status measures were available upon follow-up evaluation at 18 months for approximately 300 infants in the low-iron group, after excluding those with iron-deficiency anemia at 12 months. Even though low-iron formula was continued, by all measures the infants' iron status was better at 18 than at 12 months. Only 1.9% had iron-deficiency anemia, 17% were iron deficient, and the mean values on each individual hematologic measure improved ([Table III](#)).

Table III. Iron status of infants still receiving low-iron formula to 18 months

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Because average erythrocyte protoporphyrin levels were relatively high at 12 months, specimens from a subset of 100 children (half with high and half with low EP levels) were sent to the Centers for Disease Control, Atlanta, Georgia, for determination of lead levels. The lead levels of 50 children with high EP levels (172.4 +/- 70.3 mg/dL red blood cells) averaged 6.0 +/- 3.2 mg/dL. The lead levels of 50 infants with low EP levels (62.4 +/- 16.2 mg/dL red blood cells) averaged 6.4 +/- 2.2 mg/dL, a non-significant difference. These data confirm

that lead levels are low in urban Chilean infants, [18] even among those with high EP levels.

Absorption studies in adult volunteers demonstrated that the bioavailability of the iron in the low-iron formula was very high, averaging 38% (considering an absorption of the reference dose as 40%, as is customary to permit comparisons). Work in our laboratory showed that the bioavailability for the high-iron formula was 20%.

Discussion

This study shows that newer preparations of low-iron formula are meeting infant iron needs better than expected, even in a developing country where other sources of iron are limited in the first year of life. In this study, low-iron formula was not significantly inferior to iron-fortified formula in the prevention of iron-deficiency anemia. However, iron-deficiency anemia is a late manifestation of iron deficiency. A greater proportion of infants in the low-iron group was iron deficient at 12 months by the criterion of 2 of 3 measures of iron status in the deficient range, but mean differences in iron measures were minor from a clinical perspective. Infants in the low-iron group did not progress to iron-deficiency anemia. All indicators of iron status improved in the low-iron group by 18 months.

It is unlikely that iron sources other than formula were major influences on the infants' iron status in the first year of life. Our previous studies show consistently that other Chilean infant populations similar in socio-economic status and diet to the current sample have a low mean iron intake of 5 mg/day from solid foods, 90% of which is from vegetables with low bioavailability, such as spinach, chard, and legumes. [13] Moreover, there was concurrent evidence that the iron status of infants in the study communities who consumed cow's milk was comparable to that found in previous surveys. Immediately after the low-versus high-iron trial reported here, we studied 404 infants receiving unmodified cow's milk as part of the larger study, using similar qualifying criteria. At 12 months, the prevalence of iron-deficiency anemia and iron deficiency overall were 21% and 49%, respectively. Thus both high- and low-iron formulas in the current study were effective in decreasing the level of anemia and iron deficiency substantially below that seen in Chilean infants who receive unmodified powdered cow's milk. Previous research involving breast fed babies provides another indication that poor iron status of infants in Chile is the result of dietary limitations combined with rapid growth, rather than some other factor such as occult intestinal bleeding with ingestion of cow's milk. In a previous large study in this community, iron-deficiency anemia was common among infants who were breast fed as their sole source of milk; 15% had iron-deficiency anemia at 9 months of age. [19] Thus the foods available to young infants in Chile put them at high risk for iron-deficiency anemia, even if they do not drink cow's milk. The final piece of evidence pointing to the importance of dietary factors is our observation of improved iron status at 18 months despite continued intake of low-iron formula.

In addition to the increased dietary variety and decreased rate of growth in the second year of life, bread and other wheat-containing products are introduced in the toddler diet in Chile, where wheat is iron-fortified. [20]

Infants in the high-iron group had higher 12-month hemoglobin and ferritin levels and mean cell volumes, and lower levels of erythrocyte protoporphyrin than those in the low-iron group. This indicated that the amount of iron in the formula did affect overall iron status. Better iron status with sufficient consumption of the high-iron formula indicates that the higher level of iron in this formula permitted more iron to be absorbed as more formula was consumed. That iron status did not vary with intake in the low-iron group suggests that iron absorption was at a ceiling level.

Several considerations particular to this study may make the iron status of the low-iron group better than expected among other groups of infants:

1. All study infants weighed more than 3 kg at birth. The iron endowment of these infants thus was optimal to face the demands of the first months of life. Babies with lower birth weight, even if term, might not have fared as well.
2. The infants who had low hemoglobin levels by capillary samples at 6 months of age and confirmed as having iron-deficiency anemia by venipuncture were excluded from the study and treated with medicinal iron. This procedure meant that some infants at high risk for having iron-deficiency anemia at 12 months did not enter the trial.

3. Breast feeding was widespread and only rarely did an infant receive less than 2 months of breast milk as the exclusive source of nutrients. Even after bottle feedings were begun, most children continued to receive breast milk more than once a day. This condition of mixed milk diets has an underdefined effect on iron absorption. However, it is conceivable that breast milk facilitated iron absorption from formula, because Chilean infants usually are given both at the same meal.

4. Morbidity was very low in these children, and any illnesses were promptly treated by project medical staff. Moreover, a serious illness requiring hospitalization for longer than 5 days excluded the infant from further study participation. Thus another common cause of anemia was eliminated by design.

5. Beginning at 4 to 6 months, the solid diet of a Chilean infant is abundant in fruits and vegetables with a high content of vitamin C and vitamin A. Both high- and low-iron formulas contained these vitamins as well. Thus the infants had ample intake of vitamins that may help prevent iron deficiency and anemia.

How could the little amount of iron in the low-iron formula prevent iron-deficiency anemia? The bioavailability of iron in formula has steadily improved, [1] and the amount of iron in unfortified preparations is often above the minimum of 1.5 mg/L of elemental iron. Our laboratory has shown that iron absorption is now 20% to 22% in several iron-fortified proprietary formulas, including the high-iron formula used here. These absorption studies were conducted with formulas containing 9 to 12 mg/L of iron. The percent absorption from formula with a lower iron content would be even higher, because percent absorption increases as the amount of fortification iron decreases. [21] In fact,

the absorption of iron in the low-iron formula used in the current study averaged 38%, approaching that reported for breast milk (about 50%).

Although a greater proportion of the low-iron group had abnormal values on 2 of 3 measures of iron status, it is hard to argue that the statistically significant but slight mean differences between the low- and high-iron formula groups in this study are clinically important, particularly because the iron status of the low-iron group improved at 18 months and iron-deficiency anemia was virtually absent. As strong advocates of the importance of preventing iron-deficiency anemia, we are concerned that the results of this study could be used to justify continued use of unfortified formula. In populations of infants without optimal health and feeding, a higher proportion could be expected to show iron deficiency and anemia if given low-iron formula. Of particular concern are infants weighing less than 5 kg, who were excluded from this trial but are at higher risk for iron deficiency. Furthermore, although developmental and behavioral ill effects have been most consistently observed when iron deficiency is severe and chronic enough to cause anemia, it is still reasonable to be concerned about iron deficiency in the absence of anemia. [22] Thus high-iron formula continues to provide the best insurance that infants will continue to have normal iron status. However, additional research-both laboratory studies of bioavailability and clinical trials that determine infant iron status-is needed to determine how "high" would be optimal. Our results, combined with those of others, indicate that 12 mg/L or elemental iron may be higher than necessary to maintain good iron status and that the optimal level of fortification may be lower, somewhere between the current levels in high- and low-iron formulas. At more modest levels, theoretical concerns about iron overload, interference with immunity or absorption of other trace minerals should decrease. [21,23] Although special high-iron formula will continue to be needed for infants with lower birth weight, dual formula preparations (that is, with low- or high-iron) should be abolished for term infants, replaced by a single preparation with a modest level of iron fortification so that all infants can be protected from iron-deficiency anemia.

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