Iron Requirements During Infancy and Early Childhood

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Iron-deficiency anemia is considered to be a common nutritional deficiency disease in infants and small children, in both developing and developed countries (1–3). Anemia is the usual end point of iron deficiency, but nonheme effects also may contribute to many of the clinical manifestations. The combination of both hematologic and nonhematologic iron deficiency is responsible for clinical symptoms such as weakness, muscle fatigue, and abnormal gastrointestinal motility (4). Of most concern is the permanent developmental disadvantage that has been reported in observational studies (5,6), and there is no clear evidence that iron supplementation improves the developmental status of young anemic children (7).

Iron deficiency is preventable by appropriate dietary measures. In this chapter, I review first, the desirable iron intakes from infant and toddler foods to meet the iron requirements; second, the dietary risk factors in iron deficiency that should be considered; and third, the fact that infant formulas, follow-up formulas, and growing-up milks are excellent vehicles for iron fortification, because they are consumed by the child in bulk.

DESIRABLE INTAKES TO MEET IRON REQUIREMENTS

Term Infants

Infants and young children are at particularly high risk of iron deficiency because of the large demand for iron during a period of rapid growth and because their diet is often low in available iron. Iron reserves of the healthy, term newborn infant usually ensure an adequate supply of iron in the first 4–6 months of life. After that period, the infant becomes critically dependent on dietary iron.

The requirement for iron during the first 3 years of life consists of the desirable increment in total body iron plus the amount of iron needed to replace inevitable losses through the gastrointestinal tract and skin (4). To be absorbed, iron must enter from the intestinal lumen into the enterocyte, with subsequent transfer from the enterocyte to the circulation. Unabsorbed iron in the gastrointestinal tract includes iron that fails
to enter the enterocyte and iron that enters the enterocyte but is returned to the intestinal lumen with exfoliation of the enterocyte. A small amount of iron that is re-excreted into the lumen further contributes to intestinal iron losses (8). Per unit of body surface area, dermal losses of iron by infants (0.08 mg/day) are similar to those of adults (4).

The body iron content of a term infant at birth has been calculated to be 268 mg, and at 1 year, 377 mg. At age 1 year, 72% of the body iron is in hemoglobin, 14% in myoglobin and enzymes, and 14% stored in the reticuloendothelial system (4). When increments and losses during the first year are taken into account, the estimated daily requirement for absorbed iron is between 0.55 and 0.75 mg (4). During the second and third years of life, it is ~0.5 mg (9). Iron deficiency therefore results from failure to meet the needs for absorbed iron.

**Premature Infants**

During the third trimester of pregnancy, the growing fetus accumulates between 1.6 and 2.0 mg/kg/day of iron, and the iron concentration per unit of body weight remains quite stable (75 mg/kg) (10,11). Of the body iron, 80% is in hemoglobin, 9% in tissue (myoglobin, enzymes), and the rest in visceral organs such as the liver and spleen (in the reticuloendothelial system). After birth, there is a decrease in erythropoiesis and therefore a decrease in hemoglobin level. This decrease in hemoglobin occurs within the first 2 months of life. It represents the normal response to the transition from a hypoxic intrauterine environment to the oxygen-rich outside world and cannot be prevented by iron administration to the preterm infant. Preterm infants experience a more profound decrease in hemoglobin than do term infants. Predisposing factors are the extremely rapid growth rate of these infants (hence their rapid increase in blood volume), hyporesponsiveness of erythropoiesis to hypoxia resulting from the decrease in hemoglobin, and blood sampling for laboratory testing. At age ~1 month, there is normally a slight increase in plasma erythropoietin level, followed by an increase in reticulocytes and a gradual increase in hemoglobin concentration. During this period, storage iron decreases, as reflected by decreased serum ferritin. Sufficient dietary iron must be provided to replenish the stores to prevent subsequent iron deficiency and anemia (10,12).

It must be mentioned that our knowledge of iron requirements of the “healthy” premature infant who tolerates full oral nutrition during the first weeks of life is limited. Oski (13) estimated that, in the absence of iron supplementation and blood losses, a very low birthweight infant will remain iron replete until the birth weight has doubled, usually at age ~2 months (13). Beyond 2 months, iron intake from human milk cannot satisfy the needs of the rapidly growing premature infant, and an iron intake of between 2.0 and 2.5 mg/kg/day with formula, or provided as a supplement in the breast-feeding infant, protects such infants from becoming iron deficient (10,14,15).

Iron requirements of preterm infants receiving blood transfusions during the first few weeks of life have been studied (15b): it appears that feeding a low-iron formula (3 mg/l) during the first 5 weeks of life results in inadequate iron stores at age 14
weeks, as indicated by low serum ferritin values. Ehrenkranz (10) considered that an oral iron intake of 2 mg/kg/day in multiply transfused preterm infants was safe.

More recently, studies in premature infants receiving treatment with recombinant human erythropoietin to stimulate erythropoiesis suggest that the iron requirements are high. Several investigators have shown that erythropoietin doses of between 150 and 900 U/kg/week, starting during the first month of life, are efficient at stimulating erythropoiesis and preventing early anemia in premature infants. Daily iron intake during and shortly after treatment was between 3–6 and 18 mg/kg/day, and prevented most infants from depleting their iron stores (16–20). However, iron requirements in relation to erythropoietin treatment should be studied more precisely.

INFLUENCE OF DIETARY FACTORS ON IRON STATUS

Studies in the United States have reported a considerable decline in the prevalence of iron deficiency in infancy and early childhood over the last two decades. This has been attributed to improved feeding practices and preventive programs (21–23). The largest population-based study \((n = 1339)\) is the National Health and Nutrition Examination Survey (NHANES) III (23), carried out in the United States during 1988–1994, which reported prevalences of 9% for iron deficiency (biochemical indices or iron status abnormal) and 3% for iron-deficiency anemia (biochemical indices of iron status abnormal and hemoglobin below the population cut-off value) in children aged 1–2 years.

Only a few European studies have been based on samples representative of the general childhood population (24–26). These studies reported prevalences of iron deficiency ranging from 9% to 34%, and of iron-deficiency anemia ranging from 3% to 8% in children aged 1–2 years. Studies performed in socioeconomically disadvantaged populations have reported much higher prevalences of iron deficiency (24,27–30). Low food quality and lack of education about infant feeding are believed to be the main reasons for the high frequency of iron deficiency in these disadvantaged populations.

Recently we completed the first European multicenter study evaluating iron nutritional status at age 12 months (31). The study also assessed factors with potential influence on iron nutritional status, such as diet, infant growth, morbidity, and socioeconomic status. The study cohort was a representative subsample \((n = 488)\) of the Euro-Growth study sample (32), a well-defined, prospectively studied cohort of healthy, free-living children. The prevalences of iron deficiency and iron-deficiency anemia in this cohort were 7.2% and 2.3%, somewhat lower than those in the United States (23). We used logistic stepwise regression to study the influence of diet, infant growth, morbidity, and socioeconomic factors on the risk of developing iron deficiency and iron-deficiency anemia. The best-fitting models indicating the risk of iron deficiency and iron-deficiency anemia are indicated in Table 1, including only the significantly associated independent variables. Odds ratios and 95% confidence intervals are reported for each independent variable.
Feeding cow's milk (duration of feeding between age 0 and 12 months) was the most consistent risk factor negatively influencing iron status (Table 1). Each month of cow's milk feeding increased the risk of iron deficiency and iron-deficiency anemia by 18% and 39%, respectively. This negative influence has been demonstrated by several epidemiologic (25,33-35) and experimental studies (36,37). Cow's milk is not only a poor source of iron because of its low iron content, but also it is thought to reduce the bioavailability of nonheme iron provided by other foods because of its high calcium and casein content (38). Occult gastrointestinal blood loss provoked by cow's milk also may contribute to the higher risk of iron deficiency (39-41). Our results illustrate the singular importance of the negative effect of cow's milk compared with other dietary factors. In spite of recommendations (42) that unmodified cow's milk should not be fed before the age of 12 months, cow's milk obviously still plays a major role in infant feeding in certain areas and population subgroups. In our cohort of infants, cow's milk was responsible for most of the observed iron-deficiency anemia.

Feeding iron-fortified formulas (duration of feeding between age 0 and 12 months) and higher maternal education were significantly associated with a decreased risk (Table 1). Feeding iron-fortified formulas strongly influenced serum ferritin and therefore iron stores. In this study, formulas with an average iron level of 7-8 mg/l, as currently available in Europe, were found to protect against iron-deficiency anemia. Other dietary factors played a minor role as predictors of iron deficiency and iron-deficiency anemia. Breast feeding was found to have little impact on iron status at age 12 months, probably because it was largely confined to the first 6 months of life in this European cohort.

**IRON-FORTIFIED FORMULAS**

**Proposal to Decrease the Iron-fortification Level in Infant Formulas**

In the United States, most iron-fortified formulas provide 1.8 mg iron/100 kcal (label claim), equivalent to 12 mg iron/l at standard dilution, whereas in western Europe, the iron content of infant and follow-up formulas is between 1 and 2 mg/100 kcal, equivalent to 6-15 mg/l at standard dilutions (60-75 kcal/100 ml) (43). All
manufacturers provide somewhat more iron than indicated by the label claim, and the upper limit of iron permitted by the United States Food and Drug Administration in infant formulas is 3 mg/100 kcal (44), equivalent to ~20 mg of iron per liter at standard dilution.

Feeding of formulas with ≥12 mg iron per liter is a reliable means of preventing iron deficiency (45,46), and such formulas are widely accepted in the United States. However, because high intakes of iron may adversely affect absorption of copper and zinc (47,48) and might influence the gut microflora, it is necessary to learn more about the lowest iron-fortification levels that are an effective means of preventing iron deficiency. Clinical studies already indicate that healthy term infants receiving formulas with 6–8 mg iron per liter are able to maintain adequate iron stores until age 9 to 12 months (31,49,50). A recent prospective, blind trial compared growth, biochemical variables, and iron nutritional status of infants who were exclusively breast-fed or fed formulas with 4 mg/l Fe between birth and age 4 months (51): 136 healthy term infants were recruited and were either breast-fed or randomly assigned to one of three formulas (Table 2). The number of subjects from whom blood was collected at ages 30, 60, and 120 days also is indicated in Table 2. No difference between groups was found in hemoglobin, mean corpuscular volume (MCV) (data not shown), or serum ferritin (Table 2). None of the infants fed a formula with 4 mg/l iron had a serum ferritin value <20 μg/l, which confirms that this level of iron fortification of formula is sufficient (52).

Because knowledge of iron intake from formula without knowing about the bioavailability of the iron is of little value, the development of a realistic strategy to meet the child’s need for absorbed iron requires knowledge of the iron content and the bioavailability of iron from formula. Several studies have addressed the question of the availability to infants of iron used to fortify formulas. Saarinen and Siimes (53) determined iron absorption by whole-body counting 14 days after feeding ^59Fe-labeled, iron-fortified infant formulas to infants of age ~1 year. The difference in absorption was not significant between infants fed a formula providing iron at 6.8 mg/l and one providing 12.8 mg/l. However, whole-body counting and other methods that involve the use of radioisotopes are no longer considered acceptable to study iron absorption from modern infant formulas.

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>Breast milk</th>
<th>Nidina</th>
<th>Nan AW</th>
<th>NAN MW</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>404 (129–1122)</td>
<td>284 (159–565)</td>
<td>298 (69–590)</td>
<td>305 (92–658)</td>
</tr>
<tr>
<td>60</td>
<td>273 (44–891)</td>
<td>185 (94–305)</td>
<td>201 (49–570)</td>
<td>215 (48–441)</td>
</tr>
<tr>
<td>120</td>
<td>127 (5–528)</td>
<td>94 (26–204)</td>
<td>100 (28–243)</td>
<td>72 (22–115)</td>
</tr>
</tbody>
</table>

- **TABLE 2.** Serum-ferritin (μg/l) in infants fed breast milk or formulas with 4 mg/l iron

  | Number of subjects in the study where blood was collected at ages 30, 60, and 120 days. | d | e | f |
|---|---|---|---|---|
| Breast milk | 27, 24, 18 | 19, 16, 9 | 26, 24, 19 | 22, 16, 11 |
| Exclusive breast feeding. | 2.25 g protein/100 kcal; 4 mg/l Fe. | 1.8 g protein/100 kcal (acidified whey); 4 mg/l Fe. | 1.8 g protein/100 kcal (modified whey); 4 mg/l Fe. | Mean (range); none of the differences between groups was statistically significant. |
Current methods permit the determination of erythrocyte incorporation of iron with the use of the stable isotope $^{58}$Fe (54). For determining the bioavailability of an iron isotope from infant formula, the method is quite satisfactory. Recently Fomon et al. (55,56) used this isotope to determine erythrocyte incorporation of iron by infants (aged 168 and 196 days) fed a cow’s milk–based formula with iron at 8 or 12 mg/l (Table 3). The difference in quantity of iron incorporated into erythrocytes by infants fed the formulas with iron at 8 and 12 mg/l was not statistically significant and was nutritionally trivial. In an unpublished study by Davidsson et al. (55) (Table 3), infants received a dose of $^{58}$Fe together with a formula with an iron concentration of 1.4 mg/l. Mean erythrocyte incorporation of $^{58}$Fe was 10.6% of the dose, substantially higher than the percentages incorporated by infants fed formulas with iron concentrations of 8 or 12 mg/l (55,56). However, the amount of iron incorporated into erythrocytes averaged only 0.148 mg/day, less than half the amount incorporated by infants fed formulas with iron concentration of 8 mg/l or 12 mg/l.

We tested the hypothesis (57) that the percentage incorporation of $^{58}$Fe is higher from a whey-modified formula (1.8 g protein/100 kcal) with an iron content of 4 mg/l, but that iron incorporation is similar with an 8 mg/l or a 12 mg/l formula. Fifteen healthy infants (10 boys, five girls) were fed the study formula with an iron content of 4 mg/l, from age 112 days. Beginning at age 154 days, each infant was given 240 ml of formula labeled with 0.3 mg $^{58}$Fe on each of 3 days. Blood for iron-status indices and $^{58}$Fe enrichment was obtained before $^{58}$Fe administration, and 2 and 6 weeks later. Incorporation of $^{58}$Fe (percentage of dose) was calculated as described previously (54), and iron incorporation (milligrams per day) was calculated as percentage $^{58}$Fe incorporation $\times$ formula iron intake (milligrams per day). All infants were in good iron nutritional status as indicated by hemoglobin values (106–120 mg/l) and ferritin value (20–103 µg/l) in the normal age-specific range. Iron incorporation 2 and 6 weeks after ingestion of $^{58}$Fe averaged 0.234 mg/day (5.4%) and 0.26 mg (6.2%) (Table 3). Thus percentage incorporation of $^{58}$Fe was greater from NAN with an iron content of 4 mg/l than from the higher-iron formulas (55,56), whereas iron incorporation (mg/day) was not significantly less (57).

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of infants</th>
<th>Age (mo)</th>
<th>Iron in formula mg/l</th>
<th>Erythrocyte$^a$ incorporation (%) of dose</th>
<th>Erythrocyte$^a$ incorporation (mg/dose)</th>
<th>Test meal (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fomon et al. (56)</td>
<td>26</td>
<td>5</td>
<td>8, 0</td>
<td>3.5 (3.7)$^b$</td>
<td>0.269 (0.286)</td>
<td>3 x 240</td>
</tr>
<tr>
<td>Fomon et al. (56)</td>
<td>20</td>
<td>5</td>
<td>12, 0</td>
<td>2.5 (2.7)</td>
<td>0.291 (0.302)</td>
<td>3 x 240</td>
</tr>
<tr>
<td>Ziegler et al. (57)</td>
<td>17</td>
<td>5</td>
<td>4, 0</td>
<td>5.4 (6.2)$^b$</td>
<td>0.234 (0.260)$^b$</td>
<td>3 x 240</td>
</tr>
<tr>
<td>Davidson et al. (55)</td>
<td>10</td>
<td>5</td>
<td>1, 4</td>
<td>10.6</td>
<td>0.148</td>
<td>3 x 333</td>
</tr>
</tbody>
</table>

$^a$Fe$^{58}$ erythrocyte incorporation (8, 54) after 14 days.

$^b$Fe$^{58}$ incorporation after 6 weeks.
was a tendency to incorporate more iron into erythrocytes if serum ferritin levels were lower ($0.1 > p > 0.05$).

Recently it was shown that in 5-month-old infants, 47.4% of the iron isotope absorbed and retained in the body 2 weeks after ingestion is incorporated into erythrocytes ($8$). This number was used to calculate iron retention from NAN. Figure 1 indicates that (calculated) iron retention from NAN is 12%, which is higher than the calculated ($8$) iron retention from formulas with iron content of 8 mg/l (9%) and 12 mg/l (5%). It is of interest that $0.26 \text{ mg/day}$ iron retained from the iron-fortified formula is stored or used to build new myoglobin and iron-containing enzymes. A small part of the iron stored at 2 weeks is incorporated into erythrocytes between 2 and 6 weeks.

It also is of interest that the amounts of iron incorporated from formulas with 4–12 mg/l (Table 3, Fig. 2) are only about half the estimated amount by which total hemoglobin iron increases each day—that is, 0.5 mg ($55, 56$). This indicates that infants between ages 4 and 6 months still use storage iron for growth even when offered abundant amounts of iron with infant formula. Most probably, infants with poor iron status derive a greater proportion of iron needed for hemoglobin synthesis from the diet than do the infants summarized in Table 3, who had good iron status. Infants who are fed formula with low iron content (for example, 1.4 mg/l; Table 3) have to draw more heavily on iron stores to meet their ongoing needs for growth.

In view of the results of the clinical data ($31, 49–51, 58$) and the studies with stable isotopes ($55–57$) with 4—8 mg/l iron, discussed earlier, it is reasonable to decrease the iron content of iron-fortified infant formulas to those levels.

The Rationale for Iron-fortified Follow-on Formulas and Growing-up Milks

As already indicated, children during the second and third years of life need to retain $0.5 \text{ mg iron/day}$ (9). Early consumption of cow’s milk has already been discussed as the most important risk factor for developing iron-deficiency anemia ($25, 31, 33–35$). Daily consumption of 500 ml of follow-on formula or growing-up milk fortified with 8.0 mg/l of iron results in an iron intake of 4 mg. Assuming that 10% of iron is absorbed (4), the amount of daily absorbed iron from that source is $0.4 \text{ mg}$. Because additional iron will be consumed with other food, the child will easily meet the needs of $0.5 \text{ mg/day}$ of retained iron. There is no doubt that the use of iron-fortified formula after weaning results in adequate iron stores, which help prevent the later development of iron deficiency. However, it is not clear up to which age those formulas should be provided. Bramhagen and Axelsson (59) have recently reported that the rate of iron-deficiency anemia in 2-year-old children in southern Sweden was still as high as 7%. Feeding iron-fortified follow-on formulas (60) at that age was an important preventive measure (59); 43% of the children with normal iron nutritional status received iron-fortified follow-on formula, but only 11% of the children with iron deficiency did. Immigrant children had a higher risk of iron-deficiency anemia than did Swedish children (11% vs. 5%), and a lower percentage of those children received iron-fortified formulas (24% vs. 48%).
HOW IS THE IRON IN NAN UTILIZED BY A 5 MONTH OLD INFANT?

<table>
<thead>
<tr>
<th>INTAKE</th>
<th>(RETENTION)$^1$</th>
<th>INCORP. ERY</th>
<th>INCORP. ERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/d</td>
<td>4.36</td>
<td>0.49</td>
<td>0.23</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>12</td>
<td>5.4</td>
</tr>
</tbody>
</table>

2 weeks | 2 weeks | 6 weeks |

$0.26$ mg/d | 6.0 % | $0.03$ mg/d | 0.8 % |

storage | myoglobin | storage

FIG. 1. Intake, retention, and incorporation of $^{56}$Fe from NAN.
DAILY IRON NEED OF THE ERYTHROCYTE
(MG/D; AGE 5 MO)

from formula (stored > 14 days)

0.15 - 0.29 mg/d from formula (0-14 days)

need 0.59 mg/d

? storage iron

? other sources (e.g. solids)

FIG. 2. Daily iron needs of the erythrocyte (mg/day; age 5 months).
It seems that parents and health care clinicians should be educated about the benefits of continuing with iron-fortified formulas during the second and third years of life. It is well established that there are no known medical contraindications to iron-fortified follow-up formulas (4–36 months) and growing-up milks (older than 1 year).

FORMULAS FOR PREMATURE INFANTS: HOW MUCH IRON?

Iron absorption in premature infants as assessed by iron isotope techniques and metabolic balance studies is between 25% and 42% of intake (62–65). This seems to indicate a high demand for iron in the diet. However, iron incorporation into red blood cells ($^{58}$Fe uptake) in very low birthweight infants between ages 4 and 6 weeks was only between 4.4% and 12% of $^{58}$Fe intake (62,63). This indicates that growing premature infants receiving an iron-fortified formula (12 mg/l) would retain, at best, 0.25 mg iron/kg/day. This is substantially lower than the intrauterine accretion rate of 1.6–2.0 mg/kg/day. Unfortunately, studies in 8- to 12-week-old premature infants are not available. It seems that the growing fetus is not a good reference for iron requirements in the growing premature infant during the first 6 weeks, because the iron needs depend mainly on the production of red cells, which is low during the first month of extraterine life.

An association between iron supplementation and the occurrence of retinopathy was already discussed in 1949 (66). Sullivan et al. (67–69) proposed that, during the first few weeks of life, the developing retina is abnormally susceptible to damage by oxygen, because it is exposed to increased concentrations of ionic iron capable of catalyzing the formation of toxic oxygen species. This hypothesis implies that retinopathy of prematurity is initiated by oxygen radicals, but only in the presence of increased iron. The “oxygen plus iron” hypothesis suggests that both iron supplementation and blood transfusions (70) could be risk factors for retinopathy of prematurity. More than 90% of the preventive antioxidant activity of plasma is associated with transferrin and ceruloplasmin (71–73). Transferrin levels in plasma of premature infants are lower than those in term infants (74,75), and the iron load from hemolysis of red cells is high. Transferrin saturation values of 100% can be found in premature infants during the first days of life, and non–transferrin-bound iron has been shown to be present in the plasma of very low birthweight infants during the first 5 days after birth (76).

Melhorn et al. (77) showed that low vitamin E intake in formula (~5 IU/l) together with iron supplementation (10 mg/day) results in increased hemolysis and greater red cell fragility in premature infants with birth weights of between 1,000 and 1,500 g. The interactions between different intakes of polyunsaturated fatty acids (PUFAs) and iron by very low birthweight infants were studied by Williams et al. (78). High linoleic acid intake (32% of the fat in the formula; vitamin E/PUFA ratio, 0.9) resulted in lower hemoglobin values at 4 weeks in infants receiving an iron-fortified formula (12 mg/l) than in infants receiving a nonfortified formula (9.2 ± 1.7 vs. 11.9 ± 1.8 g/dl; $p < 0.01$). When a formula with linoleic acid levels similar to those in
breast milk was given (12.8% of the fat in the formula), and the ratio of vitamin E to PUFAs corresponded to the present recommendations [≥1 IU vitamin E/gram linoleic acid (79); vitamin E/PUFA ratio in the formula, 2.2], no differences in hemoglobin were found.

Intensive research in premature infants has provided us with substantial knowledge of their requirements for iron and its toxicity. However, it is difficult to establish guidelines for minimal and maximal values for premature formulas. Iron interacts with macronutrients such as protein and lipids: the quantity and quality of the protein in the formula influence iron absorption (80), and high iron concentrations in the formula can contribute to hemolysis if the concentrations of linoleic acid and vitamin E are inadequate (81). Therefore “compositional guidelines” for macronutrients in premature formulas should not overlook the present knowledge of micronutrients and the interactions between nutrients.

Physiologic anemia of prematurity cannot be prevented by providing dietary iron in iron-fortified formulas during the early postnatal period. However, a dietary iron intake of ~2 mg/kg/day with infant formula, starting at least when birth weight has doubled, might be necessary and is safe. Higher iron intakes than 2 mg/kg/day, which seem necessary during and after treatment with erythropoietin, should be provided by supplements. More research is needed to demonstrate the safety of providing iron-fortified formulas to preterm infants, in particular to very low birthweight infants, during the first few weeks of life. Macronutrients such as protein and lipids in the formula may influence iron absorption and metabolism.

Preterm formulas are currently regulated as exempt infant formulas and may have nutrient levels that are different from those required in term infant formulas. This allows formula manufacturers to offer innovative and safe formulas based on updated scientific knowledge. Recently the Scientific Committee for Food of the European Commission pointed out that defining composition criteria of nutritionally complete foods for medical purposes (including foodstuffs intended for premature or low-birthweight infants or both) would constitute a major block to innovation. The Infant Formula Council (IFC) indicated that the present scientific knowledge on requirements and toxicity of macronutrients and micronutrients for premature infants does not allow the proposal of “compositional regulations” for premature formulas. However, the IFC believes that scientific knowledge has advanced sufficiently to propose “compositional guidelines” for preterm formulas. It should be mentioned that, once published, compositional guidelines from the United States will be considered as the gold standard for premature formulas in many countries and thus will be relevant for formula registration in those countries.

CONCLUSIONS

Iron deficiency during infancy and early childhood results from failure to meet the needs for absorbed iron. Feeding of cow’s milk during the first year of life is the most consistent risk factor negatively influencing iron status. Feeding iron-fortified formulas is associated with a decreased risk of becoming iron deficient.
There are enough data from clinical trials and studies with stable isotopes to indicate that an iron content between 4 and 8 mg/l in infant formulas is sufficient to meet the needs for absorbed iron after weaning. Iron-fortified follow-on formulas and growing-up milks, as part of the diet of the older infant and toddler, are important means of preventing iron deficiency in that age range.

Intensive research in premature infants has provided more insight into the requirements for iron and its toxicity during the first months of life. It is not clear whether additional iron should be offered to very low birthweight infants before they double their birth weight, either by giving supplements to premature infants receiving mother’s milk or by iron-fortified formulas.

REFERENCES


56. Fomon SJ, Ziegler EE, Nelson SE, Serfass RE, Frantz JA. Erythrocyte incorporation of iron is similar in infants fed formulas fortified with 12 mg/l or 8 mg/l. *J Nutr* 1997; 127: 83–8.


**DISCUSSION**

**Dr. Zoppi:** You said that the daily requirement for iron is 0.25 mg/kg until birth weight doubles. If the requirement is by definition the minimal quantity necessary for growth, how is that determined?

**Dr. Haschke:** The requirement for premature infants is derived from $^{58}$Fe isotope-intake studies showing how much is consumed and how much is retained in the body. The approximate value is 0.25 mg/kg. In the term infants, the estimate comes both from isotope studies and from the factorial approach, which calculates how much iron is retained in the body.

**Dr. Vigi:** How much iron should be given to premature infants who are receiving erythropoietin?

**Dr. Haschke:** This depends on the size of the child, the rate of growth, and the dose of erythropoietin. There are published reports (1-5) in which weekly erythropoietin dosage has been between 150 and 900 units/kg, and the iron given ranged between 3 and 18 mg/kg per day, but I am not clear whether there are any definitive guidelines about iron intake during erythropoietin treatment. I think the most important thing is to supervise the children very closely and to increase the iron dose if there is any sign of deficiency. Large studies of erythropoietin treatment are being conducted, and I hope they will address this particular issue.

**Dr. Vigi:** What quantity of iron do you believe it would be advisable to put in a formula to give to premature infants after discharge? Do you think a specific amount is necessary, or should physicians make their own choices according to the individual situation?

**Dr. Haschke:** Although I am not clear exactly how much such babies need at that time, it is probably not more than 8 mg/l, as in term infants. This chapter is not closed; these babies probably need ≥8 mg, and they might need more, perhaps ≤12 mg/l. I do not think there are any really good studies comparing different postdischarge iron levels in infants born prematurely.

**Dr. Räähä:** Several studies have shown that 4 mg/l is sufficient during the first 6 months. What about when the infants get older and are starting on follow-on formulas or junior formulas? Would 4 mg/l be enough at that time, or is that not known yet?

**Dr. Haschke:** We must be aware that the baby, at age 4 to 6 months, receives iron from many different sources, not only from formulas. There is a variety of iron-fortified baby foods in Europe and the United States. Even if the absorption and retention rate from those foods is not very high, the babies usually get enough iron to fulfill their requirements. So the amount
of iron in follow-on formulas could probably be reduced from the 8 mg we have at present. However, I have no data on this.

Dr. Iolascon: Many factors determine the iron level in the body. As well as depending on nutrition, there is also a powerful influence of the genetic background. There is a very common polymorphism in the northern European population, and also present in the Mediterranean population, known as HFE polymorphism (that is the gene for hereditary hemochromatosis), which has an important effect on iron stores. Approximately 15% of the northern European population are affected by this mutation. It is very important that this be taken into account when evaluating serum iron in data from any large population.

Dr. Haschke: We are aware of this polymorphism, but in relation to infant nutrition, it does not affect the amount of iron needed in formulas or infant foods. It becomes important only beyond infancy.

Dr. Ziegler: You showed in your growth study that 9% of infants had anemia without indicators of iron deficiency, and the usual explanation given for this is that this anemia is due to infection, not iron deficiency. However, we recently compared formula-fed babies with breast-fed babies and found that babies fed formula (with iron fortification) had significantly higher hemoglobin levels than did the breast-fed babies. I am not so sure any longer that the infection explanation is true. Do you agree with that?

Dr. Haschke: We have a detailed history of infection during the 2 weeks before blood was taken for our iron studies, and from our analyses, the proportion of infants who had infections and were anemic without other obvious cause was significantly higher than the proportion who had no infection. So infections do play a role. I cannot answer the question about whether fortification of infant formula plays a major role. We have not looked at that, and there were not enough infants who were still breast-fed at age 12 months to answer the question.

Dr. Delmau: Up to what age do you recommend growing-up formulas?

Dr. Haschke: It is well known that gastrointestinal blood loss occurs in older infants when cow’s milk is fed. I cannot say whether this is still the case at age 18 months. I think there are not enough published data on this. But to fulfill nutrient requirements in later infancy, the only food that is given in bulk on a daily basis is milk, and if the milk contains enough iron, the probability is that the baby will receive a sufficient iron intake. Thus milk is a very proper vehicle for iron, even during the second and third years of life.

Dr. Van Biervliet: Knowing that iron stimulates the growth of enteric bacteria, do you have any data on bifidobacteria in iron-supplemented formulas?

Dr. Haschke: We recently finished a study in Chile on 4-month-old children who were either breast-fed or received iron-fortified formulas (8 mg/l). After 4 weeks of feeding, there was no difference in the bifidobacteria count between the formula-fed and the breast-fed infants. This was a big surprise. There also was no difference in the amount of lactobacilli in the stool. These were healthy normal infants, and I cannot comment on what may happen in case of disease.

Dr. La Forgia: What is your opinion about the need for iron supplementation in very low birthweight infants who have received multiple transfusions?

Dr. Haschke: That is a very common question, as transfusions are sometimes given on a daily basis. I mentioned a study in my presentation that showed that giving a formula containing 3 mg iron/l to such babies was not sufficient in the long term to meet their requirements (6). I still think this is a medical decision that has to be made on an individual basis. No formula producer can give you the right level of iron in a formula for every occasion—with or without transfusions, with or without erythropoietin, baby growing or not growing, stable or not stable, and so on. These decisions have to be made at the cot side by the physician.
**Dr. Miniello:** Fomon and a Chilean group showed that there was no statistical difference in the incidence of anemia in infants given a formula fortified with 4 mg iron/l and one with 12 mg iron/l, but there was a significant difference in biochemical iron deficiency. What happens to iron-containing enzymes during iron deficiency?

**Dr. Haschke:** We do not have a good monitoring system for this, and it may be important for brain function. However, we do know that impaired neurodevelopmental outcome seems to occur only when children are anemic. Biochemical iron deficiency *per se* appears not to be associated with long-lasting effects.

**Dr. Buonocore:** I agree with your suggestion that 4 mg iron/l is sufficient after 4 months, and also that any decision to give supplementary iron is a clinical one. That is very important. The physician must take into account the risks of giving iron. Neonates, and especially preterm neonates, are at high risk of harm from free iron. Many conditions, such as hypoxia or infection, give rise to increased amounts of free iron and hence to free radicals. Newborn infants have very low antioxidant capabilities, and that means there is a higher risk of oxidative stress in these babies. For this reason, I believe that we should be giving >4 mg iron/l only to babies who are receiving erythropoietin. We always must take account of the clinical status of the baby before giving iron.

**Dr. Haschke:** I agree.

**REFERENCES**