Iron Requirements in Infant Formulas During the First 6 Months of Life

Olle Hernell, Magnus Domellöf, and Torbjörn Lind

Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden

Human milk has unique properties, making exclusive breast feeding the best form of nourishment for infants during the first 4–6 months of life. During this period, breast milk alone covers all nutritional needs of the normal infant—that is, for energy, macronutrients, and micronutrients including iron. In affluent populations, exclusive breast feeding prevents the development of iron-deficiency anemia during the first half of infancy in healthy term infants (1,2). However, in socioeconomically disadvantaged populations, infants may be at risk of developing iron deficiency or iron-deficiency anemia if exclusively breast-fed beyond 4 months (3,4). In affluent societies, healthy term infants fed cow’s milk or formula without iron fortification seldom develop iron-deficiency anemia before age 4 months, but are at even higher risk than are breast-fed infants after that age (5,6). For this reason, most infant formulas are fortified with iron, but the optimal level of iron fortification is still an open question.

In this chapter, we review the requirement of iron during the first half of infancy, comparing breast-fed and formula-fed infants. We discuss what level of iron fortification to use in infant formulas intended for the first half of infancy, from what age fortification is needed, the differences in needs between populations in affluent and developing countries, and the possible side effects of excessive iron fortification. Although our focus is on term healthy infants, it should be noted that preterm and low-birthweight infants have higher iron requirements during the first months of life.

IRON REQUIREMENTS IN INFANCY

Total body iron at birth reflects gestational age and birth weight, and to a lesser extent the nutritional status of the mother (7) and obstetric factors such as blood loss during delivery and the timing of umbilical cord clamping (8). At birth, most of the body iron is in the form of hemoglobin. During the first weeks of life, there is a significant physiologic decline in hemoglobin as well as a shift from fetal- to adult-type hemoglobin, because there is no longer need for the same oxygen-delivering capacity when the neonate leaves the hypoxic intrauterine environment to face the oxygen-rich atmosphere. Excess red blood cells are lysed, and the released heme iron
increases the iron stores, which contributes to making the infant virtually self-reliant with regard to iron during at least the first 4 months of life. After ~4 months, however, in many infants, iron stores start to become depleted. Total body iron, which until this age has been relatively constant, must increase by some 70% from 4 to 12 months to allow synthesis of blood, muscle, and other tissues needed for rapid body growth. It has been calculated that the need for absorbed iron is ~0.1 mg/kg body weight per day for infants between ages 4 and 12 months (9), or a total iron intake of ~280 mg during the first year of life, to maintain normal iron stores (10). This requirement is higher than that during any other period of life. Whereas the typical picture of iron deficiency is perhaps the pale, weak adolescent girl (11), it is worth mentioning that, per kilogram body weight, the iron requirement of an 8-month-old infant is about 3 times that of a 14-year-old girl (9).

HISTORY OF IRON-FORTIFIED INFANT FORMULA

In 1928, Helen Mackay (12), in response to the high prevalence of anemia among infants and children in London, had already suggested that the disorder could be prevented through iron fortification of milk. During the 1950s and 1960s, iron-deficiency anemia in infancy was common in the United States, with a prevalence of >40% in inner-city populations (13,14). It was noted that bottle-fed infants who received mainly cow’s milk or unfortified infant formula were at high risk of developing anemia at the age of 5 to 9 months, and that this could be prevented by feeding iron-fortified formula (15,16). During the 1970s and 1980s, the prevalence of iron-deficiency anemia among children decreased, and this was attributed to increased use of iron-fortified infant formulas and other infant foods (17–20). However, iron-deficiency anemia in infancy is still a major public health problem, not only in developing countries (21), but also in certain populations in developed countries, among whom nonfortified formulas and unmodified cow’s milk are still widely used (22,23). Recent population data from the United States showed that 13% of 1-year-olds can be classified as iron deficient (24). Likewise, a multicenter study from 11 European centers (the Euro-Growth study) showed an overall prevalence of iron-deficiency anemia of 6% in the same age group (25). Breast feeding, iron fortification of infant foods including formulas, and the avoidance of unmodified cow’s milk in the diet of young children are key measures in combating iron-deficiency anemia, and this is reflected in the recent recommendations by the American Academy of Pediatrics (AAP) (26).

To illustrate the difficulty in interpretation of data in this field, in a Swedish study (part of the Euro-Growth study) of 1-year-old healthy, well-nourished infants (61% of whom were breast-fed at 6 months and 91% receiving iron-fortified cereal and milk-based follow-on formula), 26% had serum ferritin values <12 µg/l at age 12 months, indicating iron deficiency, and 13% had hemoglobin concentrations <110 g/l, indicating anemia (27). This could suggest that the phytate-rich diet caused impaired iron status despite sufficient iron intake. Conversely, the proportion of infants with low hemoglobin and low serum ferritin values did not differ between
Iron requirements during the first 6 months. Furthermore, only a few infants had both low hemoglobin and low serum ferritin, which casts doubt on the validity of the reference values used for hemoglobin and ferritin in infancy. Recently there also has been concern about the risk of using unnecessarily high levels of iron fortification in infant foods because of possible adverse effects (28).

Iron in breast milk and infant formula

The concentration of iron in human milk is ~0.3 mg/l, which is approximately the same as that in cow's milk, but the difference in bioavailability is at least fivefold in favor of human milk. The iron content of commercially available infant formulas varies widely, ranging from <1 mg/l in unfortified formula to as much as 15 mg/l in some iron-fortified formulas. Table 1 shows the various iron levels recommended by different authorities for use in infant formulas. It is obvious that there is no consensus with respect to the fortification level (Table 1).

In 1977, the European Society for Pediatric Gastroenterology and Nutrition (ESPGAN) recommended 7 mg/l as the minimal level, but no upper level for iron fortification was given, nor was the use of unfortified formula (0.7-1.4 mg/l) explicitly discouraged (29). The Commission of the European Commission recommends a fortification level of 3-11 mg iron/l (30), and the Life Science Research Office Report 1998, prepared for the U.S. Food and Drug Administration, recommended a minimal iron content of 0.2 mg/100 kcal (corresponding to ~1.3 mg/l) and a maximal content of 11 mg/l (31). The World Health Organization (WHO, Codex Alimentarius) recommendation is 0.5-1.5 mg/100 kcal, or 3-11 mg/l (32). The most recent recommendation from the AAP is to avoid all use of unfortified formulas, and to provide iron-fortified formula containing 4-12 mg/l to all infants who are not breast-fed or are partially breast-fed throughout the first year of life (26). In the United States, most formulas on the market are fortified at the upper level of the current recommendations—that is, 10-12 mg elemental iron/l. However, low-iron and unfortified formulas still account for 9-30% of the market share (26), whereas in Europe, infant formulas are generally fortified at lower levels (4-7 mg/l), although, as in the United States, unfortified formulas are still available and used (26,33,34).

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AAP, American Academy of Pediatrics; ESPGAN, European Society for Pediatric Gastroenterology and Nutrition; EU, Commission of the European Communities; FDA, Food and Drug Administration; WHO, World Health Organization.
ABSORPTION OF IRON FROM BREAST MILK AND INFANT FORMULA

As noted earlier, human breast milk contains a low concentration of iron, but the iron is highly available for absorption. Estimates of iron absorption from breast milk range from 12% to 70%, and a typical figure is 50%. Conversely, reported iron absorption from infant formulas and cow’s milk ranges from 2% to 19%, with an average ~10% (29). The reason for this difference is not fully understood. We briefly discuss the possible effects of calcium, protein content, and lactoferrin.

Cow’s milk contains almost 4 times as much calcium and 6 times as much phosphorus as does mature human milk. Hallberg et al. (35), studying iron bioavailability from human and cow’s milk in healthy adults, suggested that >70% of the variation in iron bioavailability could be explained by differences in calcium content (35). The clinical relevance of this is uncertain, however, as calcium and phosphorus fortification of formula have no effect on the iron status of infants (36). Casein and whey protein are the two dominating protein fractions of both human and cow’s milk, but with different proportions and absolute concentrations. In mature human milk, the relation between whey protein and casein is ~60:40, whereas in cow’s milk, it is 20:80. The effects of this difference in protein composition on iron absorption were studied by Hurrell et al. (37), who found that both bovine casein and whey protein hampered iron absorption, an effect most probably reflecting the iron-binding properties of these proteins.

Ascorbic acid is a known enhancer of iron absorption. Cow’s milk is much lower in ascorbic acid than is human milk, which may be another reason for more efficient absorption of iron from the latter (38). However, this difference is met by routinely fortifying modern formulas with ascorbic acid.

Finally, human breast milk, in contrast to cow’s milk, contains a high concentration of the iron-binding whey protein lactoferrin, which may facilitate absorption of iron from human milk. Lactoferrin has a reasonably high affinity for iron, is fairly stable against intestinal proteolytic digestion, and binds to species-specific receptors in human intestinal mucosa (39). The concentration of these receptors changes with age, and is highest during infancy.

Several studies have explored whether the addition of bovine lactoferrin to infant formula improves iron absorption. Using a 3-day iron balance technique and stable isotopes, Fairweather-Tait et al. (39) and Schulz-Lell et al. (40) studied iron absorption by infants from formulas with or without bovine lactoferrin and found no effect of the added lactoferrin. In agreement with this, when infants were fed one of three formulas with different levels of bovine lactoferrin (0.1 or 1.0 g lactoferrin/l, as compared with a formula without lactoferrin) from birth to age 5 months, there was no significant effect of lactoferrin fortification (41). Lönnernald and Hernell (33) substituted part of the iron (ferrous sulfate) with bovine lactoferrin-bound iron in a study comparing different levels of iron fortification in infant formulas fed from ages 1 to 6 months and found no difference between groups with respect to iron status at 6 months. Finally, Davidsson et al. (42), with a crossover design, specifically studied the effect of human lactoferrin. Eight infants were randomized to receive breast milk...
from their own mothers. The milk was fed both before and after treatment of the milk to remove the lactoferrin. The milks also were extrinsically labeled with a stable iron isotope, allowing quantification of the amount of iron absorbed. Unexpectedly, iron absorption was higher from the lactoferrin-reduced milk. Thus a promoting effect of lactoferrin on iron absorption so far remains to be documented.

Given that the iron content of human milk is 0.3 mg/l, 50% of the iron is absorbed, and a 4-month-old infant consumes 130 ml milk/kg/day and weighs 6 kg (that is, has a daily consumption of 780 ml of milk), then this infant will absorb 0.12 mg of iron per day. To achieve the same iron absorption from formula (assuming that 10% is absorbed), the iron content of formula would need to be fivefold higher than that in human milk—that is, 1.5 mg/l.

Fortification levels of 1.1 and 12.8 mg iron/l were compared in a study on Canadian term infants from very low-income families. The lower fortification level gave significantly lower hemoglobin and iron status at 6 months (5). In another Canadian study, Atkinson et al. (43) compared iron status in infants fed formulas fortified with iron to 1.5, 7, or 12 mg/l, respectively, and found lower serum ferritin at 6 months in the 1.5-mg group (43). In a study of healthy term Swedish infants, we found no significant difference in hemoglobin and iron status at 6 months in those infants fed a formula containing iron at 2 mg/l from age 1 month as compared with those fed a formula containing iron at 4 mg/l, or with exclusively breast-fed infants (44). This suggests that during the first half of infancy, a fortification level of 2 mg/l is sufficient for healthy term infants in an affluent society such as Sweden.

Using different assumptions [that is, 7% absorption and an iron requirement of 0.06 mg/kg/day (45)], the AAP Committee on Nutrition concluded that a formula containing 12 mg iron/l was necessary (26), although their recommended fortification level is 4–12 mg in formulas intended for use throughout infancy.

Obviously, it is difficult to make recommendations on iron fortification based only on theoretical calculations from absorption figures and estimates of iron requirements. Carefully designed and controlled clinical studies carried out in different strata of the infant population are essential to verify the adequacy of the fortification level suggested from the available absorption and requirement studies.

FROM WHAT AGE IS IRON FORTIFICATION NEEDED?

In the term infant, the average hemoglobin concentration at birth is ~160–180 g/l and decreases to a nadir of 110–120 g/l at age 1–2 months, regardless of diet. Neither in breast-fed infants nor in infants fed cow’s milk or unfortified formula does hemoglobin change significantly after the nadir has been reached until after the age of 4–6 months (15,16,46). This is in agreement with the normal term infant being born with iron stores sufficient to prevent iron-deficiency anemia during the first 4–6 months of life. Isotope studies have shown that iron from dietary sources does not appear in the circulating red cells in appreciable amounts until the age of 4–6 months, which further supports this view (47). Thus iron fortification of infant formulas intended for term infants would not be necessary before age 4 months.
Contrasting with this, it has been shown that infants are absorbing tracer already at age 2 months, or even before, which has been interpreted as if even breast-fed infants need iron supplementation from early age (48,49). Furthermore, although earlier studies showed that infants fed high-level iron-fortified formulas from the first few weeks of life increased their hemoglobin from ages 3–4 months (15,16), more recent studies with lower but different iron levels have not confirmed this (33,44). There are, however, indications that infants have immature regulation of iron absorption and hemoglobin synthesis during the first 6 months (M. Domellöf et al., unpublished observations). If so, absorption of tracer iron and the hemoglobin response to iron supplementation may not necessarily reflect a true need for exogenous iron.

The amount of total body iron at birth in term infants can vary by 300%, depending on birth weight and other factors (50). We found that there are significant differences in hemoglobin and iron status between Honduran and Swedish term, normal birth weight, exclusively breast-fed infants at 4 months (4). To allow for such variation between individuals and populations, and taking into consideration that iron-deficiency anemia is the latest stage of iron deficiency, it seems justified to recommend iron fortification of infant formulas intended for use also before age 4 months.

**CLINICAL STUDIES OF DIFFERENT LEVELS OF IRON FORTIFICATION**

Even severe iron-deficiency anemia in infancy may pass unnoticed, as symptoms such as paleness, fatigue, and developmental or behavioral disturbances are quite discreet. Impaired neurodevelopment and growth have been suggested as markers of iron deficiency or mild iron-deficiency anemia, which can be assessed and quantified in addition to the common hematologic and biochemical determinants of iron status in clinical studies of infants and children.

**Hematologic Outcome**

In the early American studies on iron fortification of infant formulas from the 1950s and 1960s, a level of 12 mg elemental iron per quarter gallon was used, corresponding to 12.7 mg/l (15,16). This amount of iron also was shown effectively to prevent development of iron deficiency and iron-deficiency anemia throughout infancy in later and methodologically more stringent studies (5,51). Saarinen and Siimes (52) used a slightly lower level of fortification, 11 mg/l, from early infancy, and showed that this resulted in significantly higher levels of serum ferritin at age 6–12 months compared with that with home-prepared cow’s milk formula.

As formulas have become increasingly adapted—that is, modified to resemble human milk more closely—several investigators have challenged the need for such high levels of fortification. Bradley et al. (53) compared formulas fortified with 12.7 or 7.4 mg of elemental iron per liter fed from early infancy to age 12 months, and showed no significant difference in growth or in iron status, except for a small but significant difference in ferritin in favor of the 12.7-mg group at 12 months (53).
authors concluded that the lower level of iron fortification could safely be used without risking development of iron deficiency. Haschke et al. (54) compared lower levels of fortification (i.e., 3 vs. 6 mg iron/l) from age 3 months in healthy term infants with those in a breast-fed control group. There was no difference in iron status at 9 months between the two formula groups. Low serum ferritin (<10 μg/l) was slightly more common in the breast-fed group at ages 6 and 9 months.

In two studies we compared iron status of healthy term infants receiving infant formula, with varying iron fortification levels, with that of exclusively breast-fed infants during the first 6 months of life. In the first study, a formula containing 4 mg iron/l was compared with one containing 7 mg/l (32), and in the second study, a formula with 2 mg iron/l was compared with one containing 4 mg/l (44). There was no significant difference in iron status between groups at 6 months in either of these studies.

**Neurodevelopmental Outcome**

Several studies have shown impaired development and behavioral disturbances in infants with iron-deficiency anemia (55,56), and in infants as well as in school children, iron deficiency can have adverse effects on cognition that are reversible with iron treatment (57,58).

Moffatt et al. (5), in their study of infants from very low income families (see earlier), also compared the effect of feeding iron-fortified (12.8 mg/l) or unfortified formula (1.1 mg/l) on developmental status. The results indicated that, apart from a difference in anemia and iron deficiency from age 6 months, psychomotor development assessed by the Bayley scales of infant development differed at ages 9 and 12 months in favor of the group fed iron-fortified formula. This difference had, however, disappeared at age 15 months, although by that time, 46% of the original cohort had been lost to follow-up. With a similar design, Williams et al. (59) randomized 100 infants at age 6 to 9 months, whose mothers had already chosen to feed them with unmodified cow’s milk, to either iron-fortified cow’s milk formula (12 mg/l) or unmodified cow’s milk up to the age of 18 months, after which both groups returned to unmodified cow’s milk until age 24 months. Both groups experienced a decrease in age-specific developmental scores as measured by the Griffith scales, but the decline was greater in the group receiving unmodified cow’s milk; the difference reached statistical significance at age 24 months but not at age 18 months. Daly et al. (22) reported the hematologic outcome of the same subjects, showing that the group receiving iron-fortified milk had significantly better iron status at all time points (i.e., ages 12, 18, and 24 months) despite switching back to the original milk at age 18 months.

Morley et al. (60) randomized 493 infants at age 9 months to continuing cow’s milk or receiving a formula containing 0.9 or 12 mg iron/l. The infants were followed up until age 18 months, when iron status and development were assessed. Although the infants that were fed the highest iron-fortified formula also had the highest serum ferritin, the authors could not show any difference in developmental score measured with the Bayley test.
Various studies have thus been performed using neurodevelopmental outcome to assess iron requirement in infancy, but so far, the results have been inconclusive. The fact that different populations have been studied at different ages with different developmental tests makes it difficult to compare the studies. In socioeconomically deprived populations in particular, iron-deficiency anemia may merely be a marker of other nutritional deficiencies, which confuse the picture (56). However, it also is possible that an early neurodevelopmental insult caused by iron-deficiency anemia may not result in detectable psychomotor delay during infancy, but symptoms such as deficits in attention and school performance may appear later.

Growth
Iron supplementation to anemic (61) or malnourished children (62,63) has resulted in improved growth, in the latter case, possibly because of decreased morbidity. Conversely, the carefully performed studies by Moffatt et al. (5), Daly et al. (22), and Morley et al. (60) resulted in significant differences in iron status between the groups but no detectable differences in growth, indicating that iron deficiency was not a growth-limiting factor in the infants they studied.

POTENTIAL NEGATIVE EFFECTS OF IRON FORTIFICATION
Iron is a known trophic factor for several pathogenic bacteria, and there also has been concern that iron supplementation in breast-fed infants might saturate human milk lactoferrin, thus diminishing its anti-infective properties (64). Parenteral iron treatment has been linked to exacerbation of malaria and with neonatal sepsis (65). For these reasons, it has been suggested that iron fortification of infant formula might increase the incidence of gastroenteritis and other infections. However, several studies have shown that this is not the case. Scariati et al. (66) assessed the relative risk of diarrhea in infants fed iron-fortified formula compared with that of infants fed a low-iron formula or breast-fed infants. Using a mail panel of 1,743 American mother–infant pairs, they prospectively assessed the type of feeding as well as diarrhea frequency from age 2 to 12 months. They found that exclusively breast-fed infants, even in a developed-country setting, had a lower risk of diarrhea compared with the formula-fed infants, but also that iron fortification of the formula did not cause an increased risk of diarrhea. Rather, for exclusively formula-fed infants, iron fortification provided a small but significant protective effect against diarrhea.

In a randomized trial in 1,600 Chilean infants, Heresi et al. (67) found that fortified milk (15 mg/l) caused no increase in the incidence of diarrhea or respiratory tract infections compared with unfortified milk. An exclusively breast-fed control group, however, had a lower incidence of both diarrhea and respiratory illness compared with the formula-fed infants.

Iron supplementation has been implicated in growth retardation, especially in iron-replete children (68,69). The reason for this is unknown, although an increased rate of infection has been suggested.
There has been concern that the iron used to fortify formula could displace other divalent ions—for example, zinc and copper. A high Fe/Zn molar ratio (that is, >2:1 in the diet), especially where the total amount of ionic species is >25 mg, has been implicated as a cause of impaired zinc absorption [for review, see Solomons (70)]. Several recent studies have included measurements of serum zinc in their biochemical assessments. Bradley et al. (53) found no difference in serum zinc or copper after 12 months of feeding formula fortified with either 7.4 or 12.7 mg iron/l (53). Similar results were reported by Haschke et al. (54) when comparing formulas with 3 and 6 mg iron/l. In our studies comparing breast-fed infants with infants fed formulas containing 7, 4, and 2 mg iron/l, serum zinc was similar in all three groups, whereas both serum copper and ceruloplasmin were lowest in the group receiving the highest level of iron fortification (33,44). This finding is in agreement with that of another study by Haschke et al. (71), showing that infants fed formula with a higher (10.1 mg/l) versus a lower (1.1 mg/l) iron fortification had a lower copper status (71). In summary, iron fortification of formulas at the levels currently used is not likely to affect zinc absorption (72), but an effect on copper absorption cannot be excluded.

Because of its pro-oxidant effects, excess iron has been implicated as a potential risk factor for cancer (28), as well as for coronary heart disease (73). Several recent studies have shown an association between dietary iron intake and increased risk of colorectal cancer in the adult population (74-76). However, a recent meta-analysis did not find support for the theory that iron intake is associated with coronary heart disease (77). These studies all were performed in adults, and data are scarce on the effects of iron supplementation or fortification of formula on oxidative stress in infants.

Hereditary hemochromatosis is a common genetic disorder, especially in individuals of European origin, affecting as many as 1 in 300 people (78). Infants and children with this disorder most often have not yet been diagnosed, and unnecessary iron supplementation or fortification might theoretically aggravate their iron overload.

We have found no conclusive proof so far that iron-fortified infant formulas confer important adverse effects. However, to minimize this risk, it seems prudent to keep the recommended level of iron fortification as low as possible, while meeting the needs for preventing deficiency.

CONCLUSIONS

The risk for an infant of iron deficiency developing depends on factors such as socioeconomic conditions, maternal nutritional status during pregnancy, birth weight, postnatal growth, duration of breast feeding, quality of complementary feeding, and the age at which complementary feeds are introduced. The risk of developing iron-deficiency anemia is low before the age of 4–6 months, but increases thereafter and probably reaches its peak between ages 12 and 18 months. Promotion of breast feeding and use of iron-fortified complementary foods seems an efficient strategy to prevent iron deficiency during infancy. When breast feeding is not possible, iron-fortified infant formulas should be used. The exact level of iron fortification in an infant
formula is probably not critical during the first few months, but becomes important after age 4–6 months when iron stores begin to be depleted. This is particularly true when the formula (or follow-on formula) constitutes a major part of the infant’s diet or when the infant consumes only small amounts of iron from other dietary sources. In populations at low risk of developing iron-deficiency anemia, a fortification level of 2 mg iron/l seems adequate, at least during the first 6 months of life. In populations at high risk of developing iron-deficiency anemia, it may be prudent to provide a slightly higher level of iron fortification during the first half of infancy, not only to prevent iron-deficiency anemia during this early period but also to prevent nonanemic iron deficiency—that is, depleted iron stores.

The fortification level of infant formulas or follow-on formulas intended for use after age 6 months must take into account the iron intake from other dietary sources, which varies between countries and populations.

FUTURE STUDIES

Future research should focus on the question of how to define anemia and iron deficiency in infancy. We need a better understanding of what biochemical indices and cut-off values to use. There also is a need to define short- and long-term physiologic outcomes such as neurodevelopmental and cognitive functions, and to optimize and standardize tests for assessing these functions. Such information should be obtained in properly designed, sufficiently powered, randomized and blinded prospective studies with breast-fed infants as a reference. Moreover, studies should be performed in different socioeconomic settings. Data on iron status, growth, morbidity, psychomotor development, and iron intake from other sources should be collected until at least age 12–18 months, and if possible, longer. Such data will allow a firmer scientific base than we have today for making recommendations about optimal levels of iron fortification in infant formulas. More research also is needed on bioavailability and interaction aspects. A better understanding of why the bioavailability of iron is greater from human milk than from current formulas will allow further improvement of formula composition and a lower level of iron fortification with even less risk of side effects.

REFERENCES

IRON REQUIREMENTS DURING THE FIRST 6 MONTHS


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IRON REQUIREMENTS DURING THE FIRST 6 MONTHS


DISCUSSION

*Dr. Haschke:* When you looked at the Swedish population, you did not say much about solid foods. There might be a substantial difference in the solids between Honduras and Sweden, where I assume most of the solids are iron fortified. Could you comment on that?

*Dr. Hernell:* From food-intake questionnaires, we have calculated that the iron intake from complementary foods was threefold higher in Sweden than in Honduras, so your assumption is correct. What is surprising to us, though, is that so far we have not really succeeded in showing that there was an impact of iron intake from complementary foods on iron status at 9 months, either in the Swedish or in the Honduran infants, which we had expected. It may be that the intake from complementary foods is too low in Honduras to have a real impact, and in Sweden, we do not see iron deficiency, which may explain the lack of visible impact. That is the only explanation that I have.

*Dr. Bachmann:* Did you look at the initial iron level, let us say 1 week after birth? Because the speed with which hemoglobin F–containing red cells are broken down will also contribute to your results, and we do not know about the cytochromes either.

*Dr. Hernell:* We did not look at that. We started our studies at age 1 or 4 months, and we do not have any earlier values than that.

*Dr. Robberecht:* Do you think there is any risk of iron overload when giving oral iron?

*Dr. Hernell:* I do not know, but I would agree with Dr. Haschke that the risk of iron overload with the levels we are using now in formulas in Europe would probably be negligible compared with what people are exposed to later in life.
Dr. Ziegler: You showed that your breast-fed placebo group had a rate of iron-deficiency anemia of 3% between ages 4 and 9 months. As iron-deficiency anemia is the severe form of iron deficiency with the potential for lasting effects, I believe that a rate of 3% is unacceptable. We generally think that breast feeding protects babies from iron deficiency, but that is not true for all babies. This 3% may be formed mostly from a small group of babies who are born with low iron stores. We observed such a baby in one of our studies; iron-deficiency anemia developed in this infant at age 5 months, and we looked back at our earlier results and found he had a ferritin of 60 ng/ml at 1 month. Dr. Haschke showed a ferritin value of 5 at 4 months, so that could be another such example. What do you think about that?

Dr. Hernell: That is exactly the point I was trying to make by doing this comparison with Honduran infants, because they have a lower birth weight, they probably have lower iron stores from birth, and they grow faster. There is quite obviously a relation between how fast you empty your iron stores and your growth rate. I think that is a major explanation as to why those infants develop iron deficiency before Swedish infants. I also agree with you that a 3% incidence of iron-deficiency anemia in Swedish breast-fed infants is too high. It is, however, possible that cut-off values for hemoglobin of 110 g/l and for ferritin of 12 μg/l are too high in this age group, which would overdiagnose iron-deficiency anemia. This should be studied.

Dr. Guandalini: May I ask a philosophical question of the experts? Why is it that Mother Nature creates a situation in which infants are not protected from iron deficiency, so that we have to intervene to avoid many infants becoming iron deficient? There is something here that escapes my understanding. Maybe we are setting the bar too high, or is Mother Nature failing to do her job?

Dr. Hernell: That is a good question. We have made mistakes in the past over the composition of human milk, so one should be very careful to make sure that the reference is correctly set. On the other hand, this obvious difference between Honduran and Swedish breast-fed infants must be kept in mind.

Dr. Haschke: May I give a philosophical answer? We have already discussed why we see so much allergy now, and one factor may be the clean environment. Likewise, iron is one of the most abundant elements, and if the children were brought up now as they were in earlier times, you would probably not see iron deficiency; in the past, they would have got their iron from many different sources that are denied to them now. That could be a factor.

Dr. Faldella: Do you suggest giving vitamin C supplements together with iron supplements in breast-fed infants after 6 months?

Dr. Hernell: We do not give vitamin C supplements in Sweden, but of course, formulas are fortified with vitamin C.

Dr. Goyens: Infection complicates the diagnosis of iron deficiency, and at the same time, iron deficiency increases the susceptibility to infection. Might this phenomenon have played a role in the results you obtained when you compared Honduras and Sweden?

Dr. Hernell: We are looking into that. That part of the study has not yet been completed.

Dr. Robberecht: Giving iron to breast-fed babies reminds me of the old story that if you give iron to a breast-fed baby, the lactoferrin will become saturated, and the milk will lose its anti-infectious properties.

Dr. Hernell: I certainly agree that we should be careful. That is a point I tried to make. If you give iron supplements in early life, you will have an increase in hemoglobin also in infants who are not iron deficient. It seems as though the feedback mechanism does not operate before ages 4 to 6 months. This should be considered in terms of protecting the infant from excess exogenous iron, and saturated lactoferrin could be a part of that.