

Medical Position Paper

Iron Metabolism and Requirements in Early Childhood: Do We Know Enough?: A Commentary by the ESPGHAN Committee on Nutrition

*Peter J. Aggett, †Carlo Agostoni, ‡Irene Axelsson, §Jean-Louis Bresson, ¶Olivier Goulet, ¶¶Olle Hernell, #Berthold Koletzko, **Harry L. Lafeber, ††Kim F. Michaelsen, ‡‡Jean-Léopold Micheli, §§Jacques Rigo, ¶¶¶Hania Szajewska, and ¶¶¶¶Lawrence T. Weaver

*University of Lancashire, Lancashire, United Kingdom; †University of Milano, Milano, Italy; ‡University of Lund, Malmö, Sweden; §Hôpital des Enfants Malades, Paris, France; ¶Hôpital Necker Enfants-Malades, Paris, France, ¶¶Umeå University, Umeå, Sweden; #University of Munich, Munich, Germany; **Free University of Amsterdam, Amsterdam, The Netherlands; ††Royal Veterinary and Agricultural University, Frederiksberg, Denmark; ‡‡CHUV University Hospital, Lausanne, Switzerland; §§University of Liege, Liege, Belgium; ¶¶¶Medical University of Warsaw, Warsaw, Poland; and ¶¶¶¶University of Glasgow, Glasgow, United Kingdom

Anemia affects approximately 42% of children younger than 5 years in developing countries and approximately 17% in industrialized countries (1). The latter are often, but not exclusively, children of ethnic minorities or socioeconomically deprived. Not surprisingly, these prevalence rates are highest during periods of rapid growth (6–24 months of age). Although, there are many other nutritional and infectious (gastrointestinal) causes of anemia, iron deficiency is often a contributory factor in many of these cases. Few surveys of anemia have applied strict criteria for defining and characterizing iron deficiency anemia (IDA) (2–4).

During the past decade, the possible association between iron deficiency, with or without anemia, and impaired cognitive and psychomotor development has been the subject of much concern. This concern has led to establishing extensive intervention programs to prevent iron deficiency in many countries. Preventing iron defi-

ciency also is a key issue in recommendations for infant feeding. Although iron is essential for optimum development in infants and children, we do not know the precise requirements or how to recognize milder forms of iron deficiency. Although we know the effect of severe deficiency and of toxic overdose, we know little about the association among iron supply and stores and the subtle effects of an inadequate iron supply. Iron deficiency may be defined in terms of reference ranges for hematologic and biochemical criteria derived from healthy populations, but we do not know how these reference thresholds correlate, if at all, with functional defects.

The criteria for IDA are based on hemoglobin (defining anemia) and measures of iron metabolism and function, such as circulating ferritin (reflecting the size of iron stores), serum transferrin (reflecting iron transport capacity), zinc protoporphyrin (ZPP, reflecting defective hemoglobin synthesis), and serum transferrin receptors (TfR, reflecting cellular need for iron) (3). However, these indicators of iron status are particularly difficult to interpret in infants and young children because of the impact of coincident changes in physiology and metabolism during growth and development, and because of the impact of infection.

For these reasons, the Committee on Nutrition recognizes a need to review critically the current literature with respect to the prevalence and consequences of iron deficiency and IDA in infants and children younger than 2 years. The main focus is on infants born at term in industrialized countries.

This article is accompanied by an invited review. Please see Doherty CP, Weaver L, Prentice AM. Micronutrient supplementation and infection: a double-edged sword? *J Pediatr Gastroenterol Nutr* 2002;34:346–352.

Received November 14, 2001; accepted November 15, 2001.

Address correspondence and reprint requests to Prof. Olle Hernell, Department of Clinical Sciences, Pediatrics, Umeå University, SE-901 85 Umeå, Sweden (e-mail: Olle.Hernell@pediatri.umu.se).

IRON METABOLISM

Iron metabolism during pregnancy adapts to ensure a supply to the placenta and fetus. Therefore, only when the mother is severely iron deficient does her iron status affect the newborn infant (4). The iron stores of the newborn also are influenced by the amount of blood transferred from placenta to fetus after delivery and before clamping the umbilical cord (5,6). This is why the cord should not be clamped until pulsation has stopped. Because most of the iron is transferred to the fetus toward the end of pregnancy, paralleling the rate of weight gain, preterm infants are born with smaller iron stores and have increased need for exogenous iron, in part also because of their rapid growth after birth (7).

Newborn, healthy, term infants with normal birth weight are born with iron stores sufficient to cover the needs for growth during the first 6 months of life (8,9). During this period, the infant needs little, if any, exogenous iron, explaining why breast-fed infants and infants fed an infant formula with only 2 mg/L show no signs of depleted iron stores during the first half of infancy (10). Consistent with this, the amount of total body iron does not change, although iron stores and iron content per kilogram of body weight decrease during the first 4 to 6 months of life, as the infant grows (11). The low content of iron in human milk (0.2–0.4 mg/L) limits the iron losses of the mother, which is especially important if the mother is iron deficient and breast-feeding is prolonged. Populations of lactating mothers in whom menstruation is suppressed tend to be in better iron balance than populations of menstruating women (12).

During the second half of infancy, the requirement for exogenous iron rapidly increases, to a concentration per kilogram of body weight higher than at any other time in life. The requirement of absorbed iron is about 0.1 mg/kg body weight daily, which is three times higher than that of menstruating pubertal girls (11,13).

Homeostasis

The major process responsible for modulating mammalian iron homeostasis is intestinal absorption, which is affected by the iron status of the individual, dietary factors, interorgan transport and uptake, and cellular use. The molecular mechanisms behind these processes are not fully understood, but a number of proteins are involved and changes in the abundance or activity of these proteins play a key role in iron homeostasis. Therefore, the role of iron regulatory proteins, which provide the molecular framework that coordinates regulation of iron metabolism, is beginning to be understood. Iron regulatory proteins bind to iron responsive elements in specific mRNA and regulate their use (14). In contrast with other trace elements, no regulated excretory pathway is involved in controlling the systemic body burden (15).

The divalent metal transporter 1 is important for iron absorption. It transfers nonheme iron across the apical membrane into the enterocyte. Divalent metal transporter 1 can transport a wide variety of divalent metal ions, including manganese, cobalt, copper, zinc, cadmium, and lead. Nonheme iron is preferentially absorbed in the ferrous form (14). Reduction of ferric iron to ferrous iron is accomplished by the acidic milieu of gastric content, by the composition of the meal (see below), and by brush border ferric reductase. Absorption seems to be regulated in various ways. One way depends on the size of the iron stores in the body, that is, the stores regulator. Iron absorption is up-regulated by a factor of two to three in iron deficiency states when compared with iron replete states. It probably acts at the level of crypt-cell programming in response to the saturation of plasma transferrin with iron (16). An erythropoietic regulatory mechanism responds to the iron requirements for erythropoiesis. The amount of iron recently consumed in the diet also can modulate absorption. For several days after ingesting a dietary iron bolus, the absorptive enterocytes are blocked for further iron absorption, which may occur even in the presence of systemic iron deficiency (16).

The type of iron given and the composition of the diet also affect iron absorption. The fractional absorption of heme iron, present only in meat, poultry, and fish, is considerably higher than absorption of nonheme iron (approximately 25% compared with 5–10%), and is less subjected to regulation (17). The iron status of the individual and dietary composition influence absorption of nonheme iron. Ascorbic acid is the most potent enhancer of nonheme iron absorption. The mechanism is probably reducing ferric to ferrous iron. Organic acids such as citric acid and fermented foods have an enhancing effect. Muscle foods (meat, fish, and seafood) also enhance absorption of nonheme iron through a “meat factor” (17), as yet unidentified. Foods may contain compounds (ligands) that strongly bind iron and therefore inhibit absorption, for example, phytates, mainly from whole grain cereals and soy protein, and phenolic compounds in tea, coffee, and cacao (18,19). Single-meal studies have shown a negative effect of calcium on iron absorption (20). However, other studies in 3- to 5-year-old children (21) and of long-term calcium supplements with meals (22) did not find a negative effect of calcium intake on iron absorption and iron status. Regulation of iron absorption seems to be immature during the first half of infancy (23).

DETERMINATION OF IRON STATUS

The World Health Organization defines the cutoff concentration for hemoglobin in defining anemia as 110 g/L until 5 years of age (24). This cutoff concentration is based on studies in young children and has been extrapolated to cover infancy because of lack of more appro-

priate data. However, several studies have indicated that this concentration may be too high. In a study of 1,175 8-month-old infants, Emond et al. (25) found that the fifth percentile for hemoglobin was 97 g/L and suggested that for British infants of this age, this value would be a more appropriate cutoff for anemia. Using the same approach, a cutoff of 100 g/L was suggested for children at 12 and 18 months of age (26). Similarly more than one third of healthy, term Swedish infants at 6 months of age had hemoglobin concentrations below 110 g/L, but less than 3% had s-ferritin less than 12 μ g/L, indicating that very few infants had depleted iron stores (27). No significant differences in hemoglobin concentrations or any other indicator of iron status were found between breast-fed infants and infants fed formula with 2, 4, or 7 mg iron/L, suggesting that all groups were receiving adequate amounts of iron (10). In another study of healthy, term infants, 29%, 32%, and 20% were anemic using the 110 g/L cutoff at 2, 6, and 9 months, respectively (28). Only 3% of the infants in this study had s-ferritin concentrations below the cutoff (12 μ g/L) at 9 months. When 105 g/L was used as the cutoff for hemoglobin concentration, the corresponding percentages were 15%, 5%, and 5%, respectively.

In a recent randomized study of the effect of iron supplements on healthy, term, breast-fed Swedish and Honduran infants, 20% of Swedish infants who did not receive supplementation had hemoglobin concentrations less than 110 g/L and 29% had ferritin concentrations less than 12 μ g/L at 9 months of age. The prevalence of iron deficiency defined as two of three abnormal iron status indexes (ferritin, mean corpuscular volume, and ZPP), with the following cutoff concentrations: ferritin less than 12 μ g/L, mean corpuscular volume less than 70 fL, and ZPP higher than 80 μ mol/mol heme was however below 3% and not further reduced in infants who were given daily iron supplements (1 mg iron/kg daily) between 4 or 6 and 9 months of age as compared with infants given placebo. Nor was there a difference in hemoglobin concentration at 9 months between the supplemented and the placebo groups (9).

Factors other than iron status affect hemoglobin concentration. Even mild viral infections and vaccinations decrease hemoglobin concentration (29,30). Furthermore, even within the normal range, the hemoglobin concentration of an infant is influenced by genetic factors (31), including gender (32). We conclude that more appropriate cutoff values to define anemia in infants and young children are necessary and that current prevalence data must be interpreted with caution.

No single standard test assesses iron deficiency in the absence of anemia. Different tests estimate different aspects of iron deficiency. S-ferritin is the most specific biochemical test because it correlates to total body iron stores, and a low s-ferritin concentration reflects depleted iron stores (33). However, apoferritin is an acute-phase reactant protein and is therefore elevated in inflamma-

tory processes (34). Consequently s-ferritin concentration in the normal range reflects adequate iron stores only in the absence of inflammation. Therefore, interpretation of s-ferritin concentrations is problematic in populations with a high incidence of infection. Interpretation of s-ferritin also is difficult at times of rapid systemic iron use, such as during rapid growth (35). The generally accepted cutoff concentration for s-ferritin below which iron stores are considered depleted is 12 μ g/L in children younger than 5 years of age (24). Newborn infants have high s-ferritin concentrations at delivery, reflecting large iron stores. After delivery, the physiologic reduction in hemoglobin (hemolysis) causes a further increase, with a fairly rapid decrease thereafter until concentration reaches a nadir at 9 to 12 months of age (33). During this period, low-birth-weight infants have lower s-ferritin concentrations, indicating smaller iron stores (11). Although s-ferritin concentrations during the first part of infancy seem to reflect relative changes in iron stores, no firm data indicate the exact cutoff for when iron stores are depleted with functional consequences. Some authors use the cutoff of 10 μ g/L for infants and young children, which is based on the distribution of s-ferritin concentrations in a large survey in the United States (NHANES III), in which the fifth percentile indicated abnormal values (36). In a large British study with more than 800 children, the fifth percentile was 16 μ g/L at 8 and 12 months, and 12 μ g/L at 18 months (25,26). Therefore, in this age group, such cutoffs are not based on functional pathophysiologic criteria, such as the determination of stainable iron in bone marrow aspirates, and concentrations below the cutoff do not necessarily reflect depleted iron stores. A cross-sectional study of 12-month-old, healthy Swedish infants supports this; 25% of infants had s-ferritin concentrations below 12 μ g/L (37), and no correlation was found between low s-ferritin and low hemoglobin concentrations. All infants were well nourished, with diets that included iron-fortified formula and meat. This study was part of the Euro-Growth Study, encompassing initially 520 healthy infants from 11 European areas. The prevalence of s-ferritin concentrations less than 12 μ g/L in the entire group was the same as in the subgroup, that is 24% (38). With a cutoff concentration of 10 μ g/L in the final analysis, which included 488 infants, 16% had ferritin concentrations below cutoff. However, using multiple criteria, only 7% were classified as iron deficient and 2.3% as IDA (39), suggesting that a cutoff concentration at 12 μ g/L for this age group does not indicate depleted iron stores. The relatively high frequency of infections after the age of 6 months further complicates the use of s-ferritin in this age group.

The value of using s-iron, s-transferrin, and s-transferrin saturation to assess iron deficiency also is limited. Diurnal s-iron and s-transferrin saturations vary considerably, with higher concentrations in the morning. Concentrations are also higher after each meal, whereas they may decrease during infections and inflammation

(2,39). Marked overlap in these indices between healthy and iron-deficient subjects also diminishes their usefulness in establishing or rejecting a diagnosis of iron deficiency (15).

Zinc protoporphyrin forms when iron supply is inadequate for heme production. Unlike with s-ferritin, infection does not affect the ZPP to heme ratio, and testing is inexpensive and easily accessible for field studies (2, 40,41). However, this indicator has not been well characterized or used extensively in infants and young children.

Measuring s-transferrin receptors (TfR) is a recent addition to the means of monitoring iron metabolism. Concentrations correlate to the tissue need for iron in human adults (42,43). Increased TfR is a sensitive response during the early development of iron deficiency. Serum TfR concentrations increase progressively as iron stores approach exhaustion, just before the onset of anemia. Another major advantage of measuring TfR is that infection or inflammatory processes (42) do not affect the assay significantly. The day-to-day variation in TfR concentration is also less than that of s-ferritin. Kits that have been on the market have different cutoff values. Because of this and other aspects of the kits, testing among studies is not fully comparable. Sufficient data do not yet exist to judge the value of s-TfR as an indicator of iron deficiency in infants and young children. Most studies that have used these kits for testing infants have included only a low proportion of infants with iron deficiency, which may explain the low correlation between low s-ferritin and high s-TfR concentrations. Recently, iron replete infants were shown to have higher concentrations than did iron-replete adults (44), indicating that age-related reference concentrations probably are necessary. Therefore, it is too early to judge the full value of this new indicator.

The use of multiple tests (36,45) only partially overcomes the limitations of single tests and is rarely an option in resource-poor settings. Iron-related tests do not all correlate closely with one another because each reflects a different aspect of iron metabolism.

IRON DEFICIENCY

Neurophysiologic effects

Iron is found throughout the brain, including the white matter. The content is lowest at birth and increases with age to reach adult concentrations only after puberty. Iron is delivered across the blood-brain barrier and to neurons through the transferrin/transferrin receptor-mediated route and perhaps other pathways. As in other tissues, cellular iron is linked to enzymes involved in producing adenosine triphosphate. More specific to brain activity, iron has a role in neurotransmission and myelin formation. Magnetic resonance studies of the brain during

childhood have shown the highest concentrations of iron in the globus pallidus, the caudate nucleus, the putamen, and the substantia nigra (46). However, most of the stainable iron, transferrin, and transferrin mRNA and TfR expression relate to oligodendrocytes active in the synthesis and maintenance of myelin. Similarly, ferritin, the most abundant iron regulatory protein within the human brain, is found mainly in oligodendrocytes and microglial cells (47).

Most information on iron deprivation and metabolism in the brain comes from studies using the rat model, in which brain development to some extent parallels development in the human in that the period of myelination and dendritic arborization is primarily postnatal, spanning from birth to the age of weaning in rats and from midgestation to 2 years in humans. Importantly, rats made iron deficient between birth and 21 days of age do not normalize their brain content, despite iron therapy, whereas rats approaching adulthood that are made iron deficient can do so (46,48). Moreover, rats with sustained early iron deficiency displayed persistent behavioral and learning defects (49). These results raised concern that iron deficiency during brain development in infants and young children may negatively affect brain iron concentration and function. Although these lasting changes currently are unexplained, they may relate to modifications in neurotransmission (50). The iron deficiency inflicted in the rat models generally has been severe, and therefore may not reflect the iron deficiency possibly associated with impaired development in infants and young children. However, even if these results in the rat model overestimate the consequences of iron deficiency on human brain function, the higher risk of iron deficiency experienced by infants and young children, between 6 and 18 months of age, overlaps the critical period for brain development (51).

Association Between IDA and Cognitive Development in Infants and Children

Many reports show an association between IDA and impaired cognitive and psychomotor development in infants and young children. These reports have attracted a great deal of attention because IDA is common in this age group. Therefore, the issue is a significant public health problem. Although, a strong association between IDA and cognitive development seem clear, the causality and the question of reversibility are not as clear. During the past decade, the issue has been critically reviewed with respect to study design (observational studies, intervention trials, and preventative trials), age, and the methodology used to assess outcome (52-56).

Most observational studies support the view that IDA rather than iron deficiency alone is associated with a lower mental developmental index or psychomotor developmental index as assessed by the Bayley scale of

development. A few studies have indicated that iron deficiency in the absence of anemia may also impair development (52,53). A dose-response effect is suspected because more severe anemia has been associated with poorer mental developmental index or psychomotor developmental index scores, or both (52). Although the bulk of evidence from observational studies supports a strong association between IDA and delayed development, these studies do not prove causality and are subject to many confounding factors. Anemic infants and children usually come from poorer segments of the population, and the possibility that IDA is a marker for other factors that contribute to poor developmental outcome cannot be dismissed (55,56). Several environmental indices, such as maternal IQ or education, stimulation at home, socioeconomic scores, occurrence of stressful events, or even growth and other nutritional deficiencies, may confound results. Conversely, hemoglobin concentrations account for a small proportion of the variation in developmental tests, and measures of the infant's environment may simply be too crude to control for the differences in stimulation and nutrition they receive (55,56).

To resolve the question of causality, intervention trials are necessary. These could be treatment trials in which infants are randomized to groups that receive either iron or placebo, or they could be preventive trials in which infants at an early age are randomized to groups that receive various levels of iron intake. Short-term, placebo-controlled treatment trials in children younger than 2 years have failed to demonstrate improvement in mental and motor development. Of five studies of longer duration, that is, 2 to 6 months (none included an anemic placebo group and all included a nonanemic untreated group for comparison) three found no significant benefit (53,54). A longer study in Costa Rica (57), which lasted 6 months, showed that the mental developmental index before treatment was lower in a group of infants with IDA compared with a nonanemic reference group and that treatment did not reverse this. Two placebo-controlled studies, one in England (58) and the other in Indonesia (59), produced inconclusive results. The former study failed to show an effect using the Denver test to assess development, whereas the latter found that the mental developmental index and psychomotor developmental index scores of children with treated anemia improved significantly compared with children in the placebo group. Therefore, this study also indicates that impaired development is reversible. Together, these studies have no uniform interpretation, although the study from Indonesia strongly supports a causal link.

Randomized, preventative trials are used to overcome the ethical problems of placebo-controlled treatment trials in infants. These fail to give conclusive evidence. In a study of Canadian infants from low-income families, randomized to diets of iron-fortified (12.8 mg/L) or iron-unfortified (1.1 mg/L) formula from 1 to 2 months of

life, benefits were found in psychomotor performance at 9 and 12 months. However, these benefits were no longer evident at 15 months. The loss of many children from follow-up at 15 months compromised the outcome of this study (60).

Two recent English studies showed contrasting results. In one study, Birmingham inner-city children were fed either cow milk or iron-fortified formula (12 mg/L) from 7.8 months (6–9 months) until 18 months of age. Thereafter, both groups were fed cow milk until 24 months of age. Using the Griffith general quotient scores, infants who received the iron-fortified formula showed significant benefits at 24 months but not at 18 months (61). Because there are many more variables in the nutritional supply of these infants than those related to iron alone, interpreting this result was difficult. One such variable may be the nutrient n-3 fatty acids, known to affect neurodevelopment (62). In the second and most recent study, 493 children were randomized to receiving either cow milk or to one of two infant formulas with 0.9 mg/L or 12 mg/L iron, from 9 to 18 months of age, when the infants' iron status and development were assessed. Although infants fed the formula with the highest iron concentration had the highest s-ferritin, no significant difference was found among the groups in prevalence of anemia and developmental scores as assessed by the Bayley test (63). This study was designed to compare mental and psychomotor performance, and indicators of iron status at 18 months in infants fed iron-fortified formula with infants fed cow milk. Therefore, iron deficiency was not included in the hypothesis, nor was it defined or assessed at the start of the intervention. Because iron status in these and other recent studies was not assessed or because varying criteria were used to define iron deficiency, comparison is a problem.

Some of these studies have raised the question of longer-term developmental outcome in infants with IDA. Indeed, children who had IDA during infancy scored lower on tests of mental and motor proficiency at 5 years of age and even 10 years of age than did those who were iron sufficient, irrespective of whether the early iron deficiency was treated or whether no sign of iron deficiency occurred during follow-up (64). Data from the Health Surveyors Programme in Israel found that lower hemoglobin concentrations at 9 months of age were associated with lower developmental and IQ scores at 5 years of age (65). These findings suggest that lower scores on developmental tests for children with IDA in infancy persist after the period of deficiency. However, as mentioned, other conditions associated closely with iron deficiency may be responsible for these observations. A recent population-based study, that linked childhood nutrition data collected by the Special Supplemental Program for Women, Infants, and Children and school records showed that early childhood anemia increased the risk of later mild or moderate mental retardation 1.28-fold for each decrement in hemoglobin con-

centration (g/L) (odds ratio, 1.28; 95% confidence interval, 1.05, 1.60). This effect was seen after controlling for the separate effects of birth weight, ethnicity, maternal education, sex, and age. In comparison, low maternal education level and very low birth weight increased the risk of mental retardation 12 and 4.6 times, respectively (66). Because the children in the study were different from the general school population (i.e., study children had more risk factors), the size of the effect may be considerably smaller in a population at lower risk. As mentioned above, epidemiologic studies only suggest, but do not prove, that early anemia causes mild or moderate mental retardation. Nevertheless, this study may be useful in estimating the long-term costs of lower achievement and special education associated with early IDA.

Linking Iron Deficiency and Cognitive Functions

Iron is an essential nutrient for normal brain development and function. As mentioned above, iron deficiency in early life can affect both myelination and neurotransmitter function, which could explain the association between iron deficiency and neurodevelopment. In addition to effects on cognitive functions, iron deficiency also may affect infant behavior. Anemic infants (11–13 months old) were observed as more unhappy, more fearful, and less attentive (67,68). Altered behavior may functionally isolate the child, which could add to impaired cognitive development. Another contributing factor could be an increased lead absorption in iron deficiency, because lead is known to negatively affect cognition. Animal studies have shown that lead absorption increases in iron deficiency (69), which may contribute to the association of iron deficiency and increased serum lead concentrations found in studies of infants and children (70). A likely explanation is up-regulation of the divalent metal transporter 1 transporter. However, even if plausible, given the role of iron in brain development and function, a causal relationship between moderate IDA and impaired cognitive development cannot be concluded from the available literature.

Other Effects of Iron Deficiency

Some studies have suggested an association between iron deficiency and breath-holding spells. Iron treatment significantly reduced the frequency of breath holding (71,72). Potential mechanisms have not been explained.

A number of studies found that several immune parameters are affected during iron deficiency, especially cell-mediated immunity and bactericidal activity of neutrophil granulocytes (73). A study of infants and young children between 6 months and 3 years of age found virtually no difference in the immune parameters studied between infants who were iron deficient and infants who

were iron replete (74). In many studies, no differences have been shown in the prevalence of infections when comparing infants and young children who are iron-deficient and iron-replete. Iron deficiency may protect against infection, perhaps because microorganisms are depleted of iron (75), but again no data from epidemiologic studies support this. Nor is there evidence that iron excess or iron supplementation is a risk factor for infection (76).

Physical work capacity is decreased significantly in IDA. The effect in individuals with iron deficiency without anemia is less clear (77). In severe anemia, the ability to regulate body temperature when exposed to cold also is decreased (78). This effect has been associated with an increase in urinary catecholamine concentrations (77). One study found increased catecholamine excretion in the urine of children who were iron deficient that returned to normal after treatment with iron (79). This suggests that the hypothermia often seen in severely malnourished children could result, at least in part, from iron deficiency.

EXCESS IRON INTAKE

Although no evidence suggests that large iron stores confer a benefit to the individual, a high daily intake of iron may have negative consequences. These include competition with respect to absorption of other minerals (80), prooxidant effects (81), and aggravating symptoms in diseases in which iron absorption is increased (82). The recent discovery of the divalent metal transporter 1 explains the competition between absorption of iron and divalent cations. Those of most relevance for infants and young children are copper and zinc. Infant formulas with high iron content may have a negative effect on copper and zinc absorption. In animal studies, absorption of iron competes with absorption of zinc and copper, and high iron intake resulted in reduced serum concentrations. In a study of term, healthy infants, an infant formula with an iron content of 7 mg/L resulted in a significant decrease in serum copper (27).

Iron is a strong prooxidant, and in theory a high intake may cause oxidative damage. However, no clinical studies demonstrate such effects in healthy, term infants. In adults, epidemiologic studies have shown an association between cardiovascular disease and size of iron stores (83) and iron intake (84). Theoretically this association could be mediated through oxidation of low-density lipoprotein particles. However, there is no proof of causality (85), and the relevance for infants and young children is unknown.

CONCLUSIONS

Iron is an essential nutrient with important physiologic roles in early life. Severe IDA has adverse effects on psychological and mental functions and well-being.

Whether iron deficiency in the absence of anemia has adverse effects on neurologic functions is not known. The available literature does not show a causal relationship between moderate IDA and impaired cognitive development, even if such an association is plausible based on studies of the role of iron in brain development and function. Until further knowledge is available, measures should be taken to prevent iron deficiency, for example, promoting exclusive breast-feeding, using iron-fortified formula when formula is required, postponing introduction of whole cow milk until the end of the first year of life, and promoting iron-rich complementary foods.

The prevalence of iron deficiency during the first 2 years of life will not be known until we have a better understanding of the homeostasis and regulation of iron metabolism during this critical period of development. We do not know what parameters and cutoff values to use to properly assess iron deficiency during the first 2 years. The cutoff values currently in use with respect to anemia (hemoglobin < 110 g/L) and depleted iron stores (s-ferritin < 12 µg/L) overestimate the prevalence of anemia and of iron deficiency.

To evaluate the possible effects of iron deficiency on cognitive development, larger and better controlled preventive intervention studies are necessary. Placebo-controlled studies aimed at correction of already manifested iron deficiency are problematic for ethical reasons, and also have the drawback that inefficacy of iron treatment can be caused by irreversible impairment, by confounding of other factors, or by nutritional deficiencies.

REFERENCES

- ACC/SCN, IFPRI. Fourth report on the world nutrition situation. SCC/SCN Geneva 2000:21–27.
- Looker AC, Gunter EW, Johnson CL. Methods to assess iron status in the various NHANES surveys. *Nutr Rev* 1995;53:246–54.
- British Nutrition Foundation. Measurement of iron status. In: *Iron: Nutritional and Physiological Significance*. The Report of the British Nutrition Foundation Task Force. London: Chapman & Hall; 1995:23–32.
- New York: The Nutritional Foundations. Dallman PR. Changing iron needs during development. In: *Iron deficiency in infancy and childhood*. Report for the International Nutritional Anaemia Consultative Group (INACG). 1979:12–7.
- Grajeda R, Perez-Escamilla R, Dewey KG. Delayed clamping of the umbilical cord improves hematologic status of Guatemalan infants at 2 mo of age. *Am J Clin Nutr* 1997;65:425–31.
- Pisacane A. Neonatal prevention of iron deficiency. *BMJ* 1996; 312:136–7.
- Oski FA. Iron requirements of the premature infant. In: Tsang RC, ed. *Vitamin and Mineral Requirements in Preterm Infants*. New York: Marcel Dekker; 1985:9–21.
- Saarinen UM, Siimes MA. Serum ferritin in assessment of iron nutrition in healthy infants. *Acta Paediatr Scand* 1978;67:745–51.
- Domellöf M, Cohen RJ, Dewey KG, et al. Iron supplementation of breast-fed Honduran and Swedish infants from 4 to 9 months of age. *J Pediatr* 2001;138:679–87.
- Hernell O, Lönnnerdal B. Iron requirements and prevalence of iron deficiency in term infants during the first 6 months of life. In: Hallberg L, Asp N-G, eds. *Iron Nutrition in Health and Disease 1996*. London: John Libbey; 1996:129–36.
- Dallman PR. Changing iron needs from birth through adolescence. In: Fomon SJ, Zlotkin SJ, eds. *Nutritional Anemias*. Nestlé Nutrition Workshop Series. 1992;30:29–38.
- Svanberg B, Arvidsson B, Björn-Rasmussen E, et al. Dietary iron absorption in pregnancy. A longitudinal study with repeated measurements of non-haem iron absorption from a whole diet. *Acta Obstet Gynecol Scand* 1975;48:43–68.
- Verster A. *Guidelines for the control of iron deficiency in countries of the Eastern Mediterranean, Middle East and North Africa*. Alexandria: WHO Regional Office for the Eastern Mediterranean; 1996.
- Einstein RS, Blemings KP. Iron regulatory proteins, iron responsive elements and iron homeostasis. *J Nutr* 1998;128:2295–8.
- Hallberg L, Sandström B, Ralph A, et al. Iron, zinc and other trace elements. In: Garrow JS, James WPT, Ralph A, eds. *Human Nutrition and Dietetics*. London: Churchill Livingstone; 2000:177–209.
- Andrews NC. Medical progress: disorders of iron metabolism. *N Engl J Med* 1999;341:1986–95.
- Engelmann MD, Davidsson L, Sandström B, et al. The influence of meat on nonheme iron absorption in infants. *Pediatr Res* 1998;43: 768–73.
- British Nutrition Foundation. Iron absorption. In: *Iron: Nutritional and Physiological Significance*. The Report of the British Nutrition Foundation Task Force. London: Chapman & Hall; 1995:3–12.
- Hallberg K, Hulthen L. Prediction of dietary iron adsorption: an algorithm for calculating absorption and bioavailability of dietary iron (vol 71, p 1147, 2000). *Am J Clin Nutr* 2000;71:119–60.
- Hallberg L, Brune M, Erlandsson M, et al. Calcium—effect of different amounts on nonheme-iron and heme-iron absorption in humans. *Am J Clin Nutr* 1991;53:112–9.
- Ames SK, Gorham BM, Abrams SA. Effects of high compared with low calcium intake on calcium absorption and incorporation of iron by red blood cells in small children. *Am J of Clin Nutr* 1999;70:44–8.
- Mimihane AM, Fairweather-Tait S. Effect of calcium supplementation on daily nonheme-iron absorption and long-term iron status. *Am J Clin Nutr* 1998;68:96–102.
- Domellöf M, Abrams SA, Lönnnerdal B, et al. Absorption of iron from breast-milk increases from 6–9 months in infants with low iron intakes. *Am J Clin Nutr* 2001;in press.
- International Nutritional Anemia Consultative group, World Health Organization, United Nations Children's Fund. *Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia*. Washington DC: ILSI Press; 1998.
- Emond AM, Hawkins N, Pennock C, et al. Haemoglobin and ferritin concentrations in infants at 8 months of age. *Arch Dis Child* 1996;74:36–9.
- Sherriff A, Emond A, Hawkins N, et al. Haemoglobin and ferritin concentrations in children aged 12 and 18 months. *Arch Dis Child* 1999;80:153–7.
- Lönnnerdal B, Hernell O. Iron, zinc, copper and selenium status of breast-fed infants and infants fed trace element fortified milk-based infant formula. *Acta Paediatr* 1994;83:367–73.
- Michaelsen KF, Milman N, Samuelson G. A longitudinal study of iron status in healthy Danish infants: effects of early iron status, growth velocity and dietary factors. *Acta Paediatr* 1995;84: 1035–44.
- Walter T, Olivares M, Pizzaro F, et al. Iron, anemia and infection. *Nutr Rev* 1997;55:111–24.
- Olivares M, Walter T, Llaguno S, et al. Modificaciones del hemograma y de los parámetros de laboratorio indicadores del metabolismo de hierro en infecciones virales leves. *SANGRE* 1993;38: 211–6.
- Siimes MA, Kallio MJT, Salmenperä L, et al. Effect of heredity on hemoglobin concentration. *J Pediatr* 1994;124:100–2.
- Domellöf M, Lönnnerdal B, Dewey KG, et al. Sex differences in iron status during infancy. *Pediatrics* (in press).
- Siimes MA, Addiego JE, Dallman PR. Ferritin in serum: diagnosis

- of iron deficiency and iron overload in infants and children. *Blood* 1974;43:581–90.
34. Cook JD, Skikne BS, Baynes RD. Serum transferrin receptor. *Annu Rev Med* 1993;44:63–74.
 35. Attila R, Siimes MA. Serum transferrin and ferritin in pubertal boys: relations to body growth, pubertal stage, erythropoiesis, and iron deficiency. *Am J Clin Nutr* 1996;63:179–83.
 36. Dallman PR, Looker AC, Johnson CL, et al. Influence of age on laboratory criteria for the diagnosis of iron deficiency anaemia and iron deficiency in infants and children. In: Hallberg L, Asp N-G, eds. *Iron Nutrition in Health and Disease*. London: John Libbey & Company; 1996:65–74.
 37. Persson LA, Lundström M, Lönnerdal B, et al. Are weaning foods causing impaired iron and zinc status in 1-year-old Swedish infants? A cohort study. *Acta Paediatr* 1998;87:618–22.
 38. Haschke F, Male C. Iron nutritional status during early childhood—the importance of weaning foods to combat iron deficiency. In: Hallberg L, Asp N-G, eds. *Iron Nutrition in Health and Disease*. London: John Libbey; 1996: 325–29.
 39. Male C, Persson LA, Freeman V, et al. Prevalence of iron deficiency in 12 month-old-infants from 11 European areas and influence of dietary factors on iron status (Euro-Growth study). *Acta Paediatr* 2001;90:492–8.
 40. Bothwell TH, Charlton RW, Cook JD, et al. *Iron metabolism in man*. Oxford: Blackwell Scientific Publication; 1979.
 41. Rettmer RL, Carlson TH, Origenes ML, et al. Zinc protoporphyrin/heme ratio for diagnosis of preanemic iron deficiency. *Pediatrics* 1999;104:e37.
 42. Cook JD, Skikne B, Baynes R. The use of serum transferrin receptor for the assessment of iron status. In: Hallberg L, Asp N-G, eds. *Iron Nutrition in Health and Disease*. London: John Libbey; 1996:49–58.
 43. Ahluwalia N. Diagnostic utility of serum transferrin receptors measurement in assessing iron status. *Nutr Rev* 1998;56:133–41.
 44. Virtanen MA, Viinikka LU, Virtanen MKG, et al. Higher concentrations of serum transferrin receptor in children than in adults. *Am J Clin Nutr* 1999;69:256–60.
 45. Cook JD, Skikne BS, Lynch SR, et al. Estimates of iron sufficiency in the US population. *Blood* 1986;68:726–31.
 46. British Nutrition Foundation. Iron, the brain and neurodegeneration. In: *Iron: Nutritional and Physiological Significance*. The Report of the British Nutrition Foundation Task Force. London: Chapman & Hall; 1995:88–92.
 47. Dallman PR, Siimes MA, Manies EC. Brain iron: persistent deficiency following short-term iron deprivation in the young rat. *Br J Haematol* 1975;31:209–15.
 48. Dallman PR, Spirito RA. Brain iron in the rat: extremely slow turnover in normal rats may explain long-lasting effects of early iron deficiency. *J Nutr* 1977;107:1075–81.
 49. Weinberg J, Brett LP, Levine S, et al. Long-term effects of early iron deficiency on consummatory behaviour in the rat. *Pharmacol Biochem Behav* 1981;4:447–53.
 50. Ruiz S, Walter T, Pérez H, et al. Effect of early iron deficiency on the rat parietal associate cortex. *Intern J Neurosci* 1984;23:161–8.
 51. Dobbing J. Vulnerable periods in the developing brain. In: J Dobbing, ed. *Brain, Behavior, and Iron in the Infant Diet*. London: Springer Verlag; 1990:1–7.
 52. British Nutrition Foundation. Iron and mental and motor behaviour in childhood. In: *Iron: Nutritional and Physiological Significance*. The Report of the British Nutrition Foundation Task Force. London: Chapman & Hall; 1995:65–78.
 53. Nokes C, van den Bosch C, Bundy DAP. The effects of iron deficiency and anemia on mental and motor performance, educational achievement, and behavior in children. An annotated bibliography. International Anemia Consultative group (INACG) publication 1998.
 54. Grantham-McGregor SM, Ani CC. The role of micronutrients in psychomotor and cognitive development. *Br Med Bull* 1999;55: 511–27.
 55. Lozoff B. Considering environmental factors in research on nutrient deficiencies and infant development. In: Perman JA, Rey J, eds. *Clinical Trials in Infant Nutrition*. Nestlé Nutrition Workshop Series, Nestec Ltd. Philadelphia: Vevey/Lippincott Raven Publishers; 1998;40:203–18.
 56. Lozoff B. Has iron deficiency been shown to cause altered behavior in infants? In: Dobbing J, ed. *Brain, Behavior and Iron in the Infant Diet*. London: Springer Verlag; 1990:107–31.
 57. Lozoff B, Wolf AW, Jimenez E. Effects of extended oral-iron therapy on infant developmental test scores. *J Pediatr* 1996;129: 383–9.
 58. Aukett MA, Parks YA, Scott PH, et al. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child* 1986;61:849–57.
 59. Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deficient anemic infants treated with iron. *Lancet* 1993;341:1–4.
 60. Moffatt MEK, Longstaffe S, Besant J, et al. Prevention of iron deficiency and psychomotor decline in high-risk infants through use of iron-fortified infant formula: a randomised clinical trial. *J Pediatr* 1994;125:527–34.
 61. Williams J, Wolff A, Daly A, et al. Iron supplemented formula milk related to reduction in psychomotor decline in infants from inner city areas: randomised study. *BMJ* 1999;318:693–8.
 62. ESPGAN Committee on Nutrition. Comment on the content and composition of lipids in infant formulas. *Acta Paediatr Scand* 1991;80:887–96.
 63. Morley R, Abbott R, Fairweather-Tait S, et al. Iron fortified follow on formula from 9 to 18 months improves iron status but not development or growth: a randomised trial. *Arch Dis Child* 1999; 81:247–52.
 64. Lozoff B, Jimenez E, Hagen J, et al. Poorer behavioural and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 2000;105:e51.
 65. Palti H, Peysner B, Adler B. Does anemia in infancy affect achievement on developmental and intelligence tests? *Hum Biol* 1983;55:189–94.
 66. Hurtado EK, Claussen AH, Scott KG. Early childhood anaemia and mild or moderate mental retardation. *Am J Clin Nutr* 1999;69: 115–9.
 67. Delinard A, Gilbert A, Dodds M, et al. Iron deficiency anemia and behavioural deficits. *Pediatrics* 1981;68:828–33.
 68. Deinard AS, List A, Lindgren B, et al. Cognitive deficits in iron-deficient and iron-deficient anemic children. *J Pediatr* 1986;108: 681–9.
 69. Crowe A, Morgan EH. Interaction between tissue uptake of lead and iron in normal and iron deficient rats during development. *Biol Trace Elem Res* 1996;52:249–61.
 70. Wright RO, Shannon MW, Wright RJ, et al. Association between iron deficiency and low-level lead poisoning in an urban primary care clinic. *Am J Public Health* 1999;89:1049–53.
 71. Mocan H, Yildiran A, Orhan F, et al. Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child* 1999; 81:261–2.
 72. Daoud AS, Bathiea A, al-Sheyyab M, et al. Effectiveness of iron therapy on breath-holding spells. *J Pediatr* 1997;130:547–50.
 73. Dallman PR. Iron deficiency and the immune response. *Am J Clin Nutr* 1987;46:329–34.
 74. Thibault H, Galan P, Selz F, et al. The immune response in iron-deficient young children: effect of iron supplementation on cell-mediated immunity. *Eur J Pediatr* 1993;152:120–4.
 75. Oppenheimer SJ. Iron and infection: the clinical evidence. *Acta Paediatr Scand* 1989;361(suppl):53–62.
 76. Heresi G, Pizarro F, Olivares M, et al. Effect of supplementation with an iron-fortified milk on incidence of diarrhea and respiratory infection in urban-resident infants. *Scand J Infect Dis* 1995;27: 385–9.
 77. British Nutrition Foundation. Effect of iron on work performance,

- and thermogenesis. In: *Iron: Nutritional and Physiological Significance*. Report of the British Nutrition Foundation Task Force. London: Chapman & Hall; 1995:54–7.
78. Brigham D, Beard J. Iron and thermoregulation: a review. *Crit Rev Food Sci Nutr* 1996;36:747–63.
79. Voorhes ML, Stuart MJ, Stockman JA, et al. Iron deficiency anaemia and increased urinary norepinephrine excretion. *J Pediatr* 1975;86:542–7.
80. Solomons NW. Competitive interaction of iron and zinc in the diet: consequences for human nutrition. *J Nutr* 1986;116:927–35.
81. Schneider BD, Leibel EA. Regulation of mammalian iron homeostasis. *Curr Opin Clin Nutr Metab Care* 2000;3:267–73.
82. Lynch JR. Iron overload: prevalence and impact on health. *Nutr Rev* 1995;53:255–60.
83. Sullivan JL. Iron and the sex difference in heart disease risk. *Lancet* 1981;1:1293–4.
84. Ascherio A, Willett WC, Rimm EB, et al. Dietary iron intake and risk of coronary heart disease among men. *Circulation* 1994;89:768–73.
85. Danesh J, Appleby P. Coronary heart disease and iron status: meta-analysis of prospective studies. *Circulation* 1999;99:852–4.



LIPPINCOTT
WILLIAMS & WILKINS

**Unauthorized Use
Prohibited**