

## IRON AND BREASTFEEDING

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Iron is an essential nutrient during infancy. For many years, there has been significant controversy about the adequacy of human milk in maintaining optimum iron nutrition status. This article considers the iron content of infants' diets, their iron absorption, and iron requirements, and the adequacy of human milk-feeding in infants is discussed. The limitations of present knowledge and the most important directions of future research are also considered.

### HISTORICAL OVERVIEW

Iron was well known to the ancient Greeks, and it has been known to be a component of blood for more than 200 years.<sup>49</sup> Landmark studies by MacKay in the 1920s in the East End of London put the study of iron deficiency in infants on a firm scientific foundation.<sup>47</sup> MacKay showed progressive anemia in infants after at approximately 5 months of age, especially in infants fed artificial formulas, with human milk-feeding being relatively protective. She also showed that this anemia could be prevented by, or treated with, inorganic iron salts and that treatment of anemia had other beneficial effects, including a decrease in respiratory illnesses.<sup>47</sup>

### CONSEQUENCES OF IRON DEFICIENCY

Iron deficiency occurs in several stages.<sup>15</sup> If iron requirements exceed iron intake, the deficit initially is compensated by the mobilization of iron stores from ferritin, a stage described as decreased iron stores<sup>15</sup> or iron depletion. This stage is reflected as decreasing plasma ferritin values. After iron stores are exhausted, persisting negative iron balance leads to a decrease in hemoglobin

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Table 1. IRON-DEPENDENT ENZYMES

Enzyme	Function
Heme-containing proteins	
Hemoglobin	Oxygen transport
Myoglobin	Oxygen storage in muscles
Cytochromes a, b, c	Electron transport and ATP production
Cytochrome P-450	Degradation of endogenous/exogenous toxins
Tryptophan-1,2-dioxygenase	Pyridine metabolism
Catalase	Degradation of hydrogen peroxidase
Myeloperoxidase	Electron donor
Iron metalloproteins	
Aldehyde oxidase	Electron transport
NADH dehydrogenase	Energy metabolism
Tyrosine hydrolase	Dopamine, serotonin, noradrenaline synthesis
Succinic dehydrogenase	Energy metabolism
Prolyl hydroxylase	Collagen synthesis
Tryptophan hydrolase	
Xanthine oxidase	Electron transport
Enzymes requiring iron as a cofactor	
Ribonucleotide reductase	RNA and DNA synthesis
Phosphoenolpyruvate	Gluconeogenesis
Aconitase	Tricarboxylic acid cycle

NADH = Nicotinamide adenine dinucleotide phosphate.

and iron metalloenzyme synthesis. These enzymes (Table 1) are vital components of many metabolic pathways. During this phase of iron deficiency, the hemoglobin concentration may remain within the normal range for some time, and a stage of iron deficiency without anemia exists. The plasma ferritin level may be low ( $< 10 \mu\text{g/L}$ ), and the transferrin saturation may decrease. Finally, after a sufficiently prolonged period, hemoglobin synthesis is compromised sufficiently for the measured hemoglobin concentration to decrease to less than the lower limit of normal ( $> 2$  standard deviations [SD] less than the age-specific mean hemoglobin concentration), and iron-deficiency anemia may be diagnosed.

Iron-deficiency anemia is characterized by a microcytic hypochromic anemia<sup>74</sup> and may be confirmed by a low plasma ferritin<sup>12</sup> or an elevated serum transferrin receptor level.<sup>13</sup> It is important that age-specific values are used to define anemia in infants<sup>52</sup> because there are complex changes in hemoglobin concentration after birth.<sup>16</sup> Hemoglobin concentration is typically high at birth and decreases over the next 1 or 2 months because of low erythropoiesis. As the nadir is approached, erythropoiesis increases rapidly, and hemoglobin concentration begins to increase again.<sup>16</sup> At its nadir, hemoglobin concentrations of less than 10 g/dL are not uncommon.<sup>32, 52</sup>

There are several well-designed, large cohort studies showing that iron-deficiency anemia may lead to developmental delays in 1- to 2-year-old children and that these deficits may not respond to even prolonged iron therapy.<sup>46, 68</sup> Reassuringly, iron deficiency in the absence of anemia does not seem to have adverse developmental consequences.<sup>46, 68</sup> Lozoff et al<sup>45</sup> have suggested that children with iron-deficiency anemia show behaviors that could contribute to "functional isolation," including being more wary, hesitant, easily tired, and were less playful. Whether these findings explain the adverse effect of iron deficiency on developmental outcome, or whether this effect is caused by changes in neurotransmitter synthesis, receptor number, or function, is unclear.

Table 2. IRON ABSORPTION MEASUREMENTS IN TERM, BREASTFED INFANTS

Results (%)

No. Subjects

Method

Study

**Function**

in muscles  
 t and ATP production  
 endogenous/exogenous toxins  
 ism  
 hydrogen peroxidase

rt  
 sm  
 nonin, noradrenaline synthesis  
 sm  
 isis

synthesis  
 d cycle

able 1) are vital components  
 on deficiency, the hemoglo-  
 ange for some time, and a  
 lasma ferritin level may be  
 y decrease. Finally, after a  
 is compromised sufficiently  
 ease to less than the lower  
 than the age-specific mean  
 nia may be diagnosed.  
 icrocytic hypochromic ane-  
 itin<sup>12</sup> or an elevated serum  
 -specific values are used to  
 lex changes in hemoglobin  
 on is typically high at birth  
 f low erythropoiesis. As the  
 and hemoglobin concentra-  
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studies showing that iron-  
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**Table 2. IRON ABSORPTION MEASUREMENTS IN TERM, BREASTFED INFANTS**

Study	Method	No. Subjects	Results (%)
Feuillen (1954) <sup>31</sup>	Radioisotope	2	Range, 45-75
Garby (1959) <sup>33</sup>	Radioisotope	12	Range, 15-96
Gorten (1963) <sup>34</sup>	Radioisotope	14 preterm infants, 1-10 wk old	Mean, 31.5; range, 6.8-74.0
Saarinén (1977) <sup>61</sup>	Radioisotope	45, 5.9-7.3 mo	Mean, 49
Dauncey (1978) <sup>20</sup>	Balance	2, SGA	HM maintained positive iron balance
Schulz-Leil (1987) <sup>62</sup>	Balance	6, 15-17 d postnatal	Mean, 32.8 (SD, 42.5)
		9, 35-38 d postnatal	Mean, 39.2 (SD, 13.1)
		8, 57-60 d postnatal	Mean, 58.4 (SD, 48.6)
		9, 85-89 d postnatal	Mean, 71.3 (SD, 27.6)
		7, 110-115 d postnatal	Mean, 46.4 (SD, 33.5)
Davidsson (1994) <sup>22</sup>	Stable isotope	5, 2-10 mo	Mean, 11.8 (range, 3.4-37.4)
Abrams (1996) <sup>4</sup>	Stable isotope	14, 5-7 mo	Mean, 20.7 (SD, 14.8)

SGA = Small for gestational age; HM = human milk.

## CONSEQUENCES OF IRON EXCESS

Iron is essential for the growth of microbes and malignant cells, and eukaryotic have developed mechanisms to "withhold" iron from such competitors.<sup>69,70</sup> Biologic fluids contain several proteins that chelate iron and keep it in a form in which it may be absorbed by the host but is unavailable to microbial, or neoplastic, cells. A classic example of this is lactoferrin, a transferrin-like, iron-binding protein abundant in human milk<sup>6</sup> the iron-withholding function of which may contribute to a lower prevalence of enteric infections in human milk-fed infants. Some evidence shows that high iron status may be a risk factor for certain malignancies, presumably because iron availability is no longer a rate-limiting factor for neoplastic cell growth<sup>38, 40, 53, 66</sup>; however, the relevance of this risk to infants is unclear, and iron supplementation during infancy is unlikely to significantly increase lifelong iron burden.

More clear is the effect of parenteral iron dextran on infections in infancy. When used routinely to prevent iron deficiency, it increases the prevalence of severe sepsis by approximately 20-fold<sup>5</sup> and increases the prevalence and severity of malaria.<sup>54</sup> One prospective study has, however, found no effect of *enteral* iron (namely, an iron-fortified formula) on infections in term infants.<sup>64</sup>

Many of the biologic functions of iron are caused by its ability to exist in oxidized ( $\text{Fe}^{2+}$ ) and reduced ( $\text{Fe}^{3+}$ ) forms. This ability also explains its potentially toxic effect as a producer of free radicals. Iron may act as an electron donor and may produce toxic hydroxyl ( $\text{OH}\cdot$ ) radicals.<sup>36</sup> Mammalian systems have developed a system to bind iron by chelators, such as transferrin, which prevent redox cycling<sup>65</sup> and the detrimental effects that may result.<sup>24, 65</sup> Whether redox cycling iron and its resultant free radicals have clinical consequences for full-term infants is unclear, but there is significant concern regarding excess iron and free radicals as risk factors for conditions such as bronchopulmonary dysplasia and necrotizing enterocolitis in preterm infants.

## IRON CONTENT OF HUMAN MILK

The iron content of human milk is highest in early transitional milk (0.97 mg/L)<sup>67</sup> but decreases steadily during lactation, reaching a level of approximately 0.3 mg/L by age 5 months.<sup>63</sup> Iron intake from human milk averages 0.075 mg/kg at 1 month, 0.055 mg/kg at 2 months, and 0.048 mg/kg by 3 months of age.<sup>44, 67</sup> There is, however, a wide inter- and intraindividual variability.<sup>58</sup> The iron content of human milk does not seem to be affected significantly by the mother's iron status, maternal iron deficiency, or maternal iron therapy.<sup>10, 75</sup>

Human milk is a complex system, and the distribution of iron within different compartments within human milk reflects this complexity. Although estimates vary, 2% to 10% of iron is present in the casein; 65% to 81%, in whey; and 19% to 26%, in the fat.<sup>39</sup> A significant proportion of the iron in the milk fat globule is in the form of xanthine oxidase, one molecule of which contains eight atoms of iron.<sup>42</sup> The other major iron-binding ligand in human milk, lactoferrin, has a typical iron saturation of less than 5%<sup>42</sup> but still contains a significant amount of iron.<sup>42</sup> Although it may be important in iron withholding defenses, its role in iron absorption is less clear.<sup>22, 23, 51</sup>

## IRON ABSORPTION FROM HUMAN MILK

A typical estimate of iron absorption from human milk is approximately 50%.<sup>2, 41</sup> (Table 2); however, two studies using stable isotopes have questioned

this high value<sup>4, 21</sup> and have reported but these values cannot be compared with those from older infants, including studies where values were obtained using extrinsic iron.

Even taking a high estimate, assuming an iron intake from human milk of 0.04 mg/kg per day is absorbed, only 0.02 mg/kg per day is required for growth, and these iron requirements are met until dietary iron intake increases.

## OTHER SOURCES OF IRON

Other sources of iron during infancy include milk during supplementary formula feeds, and iron-fortified weaning foods. It is suggested that the addition of iron to weaning foods from human milk,<sup>56</sup> but iron-fortified weaning foods have little impact on iron status in infants if iron is not absorbed.

Initially iron fortification was limited by the low bioavailability, to the food source. However, the addition of vitamin C has improved greatly the bioavailability of iron. Vitamin C has been shown to further increase iron absorption by consuming iron-fortified weaning foods, resulting in a twofold increase in iron absorption.<sup>60</sup> Iron-fortified weaning foods is typically 0.6 mg/kg per day at 9 months.<sup>37</sup> One study in Honduras found that iron-fortified weaning foods in old infants to continue exclusive breastfeeding into the diet. By 9 months, iron-fortified weaning foods had a significant impact on the exclusively breastfed group (lower iron concentrations, hematocrits, and plasma ferritin was low among infants weighing more than 3 kg but more common in infants weighing less than 3 kg).<sup>25</sup> Iron-fortified weaning foods in infants with nutritional status in breastfed infants seem to be at increased risk for lower iron endowment at birth and slower growth. Iron-fortified weaning foods intake of a highly bioavailable form of iron has a significant positive impact on iron status.

As early as the 1920s, the use of iron-fortified cow's milk was identified as a risk factor for iron deficiency. Despite advice against its use, cow's milk was given to infants.<sup>71</sup> In the United Kingdom, the practice of giving cow's milk to infants receive cow's milk, but 42% of infants (1990 data).<sup>71</sup> This practice seems to have declined since 1985 was 67%.

this high value<sup>4,21</sup> and have reported absorption fractions of approximately 20%, but these values cannot be considered definitive because they were obtained from older infants, including some who were receiving mixed feedings, and were obtained using extrinsic iron labeling.

Even taking a high estimate of iron absorption from human milk (50%) and assuming an iron intake from human milk of 0.075 mg/kg per day,<sup>67</sup> less than 0.04 mg/kg per day is absorbed by term infants. This amount is much less than required for growth, and these infants therefore are largely dependent on stored iron until dietary iron intake increases.

### OTHER SOURCES OF IRON

Other sources of milk during the first year of life include weaning foods, supplementary formula feeds, or cow's milk feeds. Early research in adults suggested that the addition of weaning foods might decrease iron absorption from human milk,<sup>56</sup> but iron-fortified weaning foods could have a positive impact on iron status in infants if the iron added to them was sufficiently well absorbed.

Initially iron fortification was achieved by the addition of iron salts, often of low bioavailability, to the food.<sup>57</sup> The change to small-particle electrolytic iron has improved greatly the bioavailability of iron from infants' cereals,<sup>57</sup> and vitamin C has been shown to further increase iron bioavailability.<sup>30</sup> For example, consuming iron-fortified weaning foods with a vitamin C-rich drink leads to a twofold increase in iron absorption.<sup>29</sup> Iron-fortified weaning foods have become increasingly available,<sup>60</sup> and by age 6 months, the iron intake from iron-fortified weaning foods is typically 0.6 mg per day, increasing to 2.4 mg per day by age 9 months.<sup>37</sup> One study in Honduras<sup>25</sup> randomized exclusively breastfed 4-month-old infants to continue exclusive breastfeeding or to introduce iron-fortified weaning foods into the diet. By 6 months of age, the group consuming iron-fortified weaning foods had a significantly greater iron intake (4 mg/d) than did the exclusively breastfed group (0.2 mg/d) and significantly higher hemoglobin concentrations, hematocrits, and plasma ferritins.<sup>25</sup> The prevalence of anemia or low plasma ferritin was low among infants whose birth weights were greater than 3 kg but more common in infants of lower birth weights. Of the exclusively breastfed infants, the prevalence of anemia was approximately 10% in infants of birth weight more than 3 kg but almost 50% in the infants born weighing less than 3 kg.<sup>25</sup> Iron-fortified weaning foods, therefore, seemed to improve iron nutritional status in breastfed infants; however, infants of lower birth weights seem to be at increased risk for iron deficiency, presumably because of their lower iron endowment at birth and their increased iron requirements for catch-up growth. Iron-fortified weaning foods, therefore, may represent a significant intake of a highly bioavailable form of iron during infancy and could have a significant positive impact of iron nutrition in infants.

As early as the 1920s, the consumption of homemade infant formulas was identified as a risk factor for iron deficiency in infants<sup>47</sup>; the same seems to be true of cow's milk, which seems to increase the risk for iron deficiency.<sup>2, 18</sup> Despite advice against its use, cow's milk is fed to a significant number of infants.<sup>71</sup> In the United Kingdom, less than 5% of 4- to 5-month-old infants receive cow's milk, but 42% of infants aged 9 to 10 months receive cow's milk (1990 data).<sup>71</sup> This practice seems to be decreasing; the corresponding figure in 1985 was 67%.

### ESTIMATED IRON REQUIREMENTS OF HUMAN MILK-FED INFANTS

Iron requirements in infants may be estimated using a factorial approach that exploits the knowledge of the iron content of lean tissues and hemoglobin.<sup>27, 32, 55</sup> Table 3 summarizes the average hemoglobin concentration during the first year of life<sup>32</sup> and the average weight of breastfed infants.<sup>72</sup> The iron content of lean tissues is approximately 7 mg/kg, so the tissue iron mass may be estimated by multiplying this number by an infant's weight. The circulating hemoglobin mass may be calculated from the weight, hemoglobin concentration, and blood volume (typically 75 mL/kg). In turn, this result may be converted to a hemoglobin iron mass because each gram of hemoglobin contains 3.47 mg of iron.<sup>27, 55</sup> The iron content of newborn infants is approximately 75 mg/kg.<sup>27, 73</sup> By 1 month of age, only approximately 200 mg of iron is required to meet the needs for lean body mass and circulating hemoglobin (the sum of tissue iron mass and hemoglobin iron mass, Table 3). It is not until after 4 months of age that the total body iron mass exceeds that present in newborn infants. Table 3 is modified to take into account iron that might be absorbed from the diet in exclusively human milk-fed infants. Two sets of assumptions are used: (A) a conservative one that assumes that iron intake from breast milk is 0.048 mg/kg per day, and iron absorption, 20% and (B) a more generous one, in which iron intake from breast milk is 0.075 mg/kg per day, and iron absorption, 50%. These calculations ignore any iron losses, which are usually small but may be modified to account for storage iron.<sup>32</sup> Although crude, and ignoring the biologic variability of iron content at birth, these calculations are used widely<sup>27, 32, 55</sup> and suggest that newborn infants are unlikely to become iron deficient in early infancy. Using the more conservative estimate (Table 3, B) human milk would be expected to meet the iron needs of infants until 6 months, or 12 months based on the more generous assumptions (Table 3, A).

### ADEQUACY OF HUMAN MILK

In a study of 25 infants exclusively breastfed to 6 months of age and 15 formula-fed infants weaned at 2 to 3 months of age, Calvo et al<sup>8</sup> showed no overall difference in hemoglobin concentration between the two groups but a lower serum ferritin in the 9-month-old, breastfed infants. Also, anemia (hemoglobin < 11 g/dL) and iron deficiency (serum ferritin < 10 µg/L) were significantly more common in the 9-month-old, breastfed infants. Almost 28% of the breastfed infants were anemic at 9 months of age, compared with only 7% of the infants fed formula, but this definition of *anemia* is relatively strict, and although vitamin C and iron-rich weaning foods were encouraged, iron-fortified weaning foods were not allowed.

Duncan et al<sup>26</sup> studied 33 infants who were exclusively breastfed for the first 6 months of life and received no formula or weaning foods during this time. None of the infants became anemic, although 12% had low mean cell volumes at 6 months of age, and 3% had low serum ferritin values. A smaller study involving 10 infants exclusively breastfed to 5 months of age, without weaning foods or iron supplementation, showed that 2 infants (20%) were anemic by age 90 days.<sup>11</sup> Haschke et al<sup>37</sup> studied 30 breastfed infants who began weaning at 90 days of life. By 6 months of age, 13% of the breastfed infants were iron deficient (serum ferritin < 10 µg/L), decreasing to 3% by age 9 months. Lönnerdal and Hernall<sup>43</sup> compared 10 breastfed infants to four groups of formula-fed infants. No iron-containing weaning foods were used before age 6

Table 3. IRON REQUIREMENTS OF HYPOTHETICAL MALE INFANTS ESTIMATED USING A FRACTIONAL METHOD

Age (mo)	Hb* (g/dL)	Weight (kg)	Tissue Iron (mg)†	Hb-iron (mg)‡	Total Body Iron (mg)§	Iron Requirement Since Birth		TBI, and Absorbed Iron	
						mg/d	mg/kg/d	A	B
0	14.5	3.49			262¶			262	262
1	14.1	4.58	32.1	168.1	200	-2.05	-0.51	263	266
2	11.4	5.50	38.5	163.2	202	-1.00	-0.77	274	277

ated using a factorial approach of lean tissues and hemoglobin.<sup>27</sup> concentration during the first d infants.<sup>72</sup> The iron content of ue iron mass may be estimated ht. The circulating hemoglobin globin concentration, and blood may be converted to a hemoglo- n contains 3.47 mg of iron.<sup>27, 55</sup> tely 75 mg/kg.<sup>27, 73</sup> By 1 month e required to meet the needs for e sum of tissue iron mass and after 4 months of age that the or infants. Table 3 is modified ed from the diet in exclusively ns are used: (A) a conservative lk is 0.048 mg/kg per day, and one, in which iron intake from orption, 50%. These calculations ut may be modified to account e biologic variability of iron idely<sup>27, 32, 55</sup> and suggest that cient in early infancy. Using the nk would be expected to meet 2 months based on the more

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1	14.1	4.58	32.1	168.1	200	-2.05	-0.51	263	266
2	11.4	5.50	38.5	163.2	202	-1.00	-0.22	264	272
3	11.2	6.28	44.0	183.1	227	-0.39	-0.08	266	279
4	11.5	6.94	48.6	207.7	256	-0.05	-0.01	268	286
5	11.5	7.48	52.4	223.9	276	0.10	0.02	270	295
6	11.5	7.93	55.5	237.3	293	0.17	0.03	293	303
9	11.8	8.89	62.2	273.0	335	0.27	0.04	300	332
12	11.9	9.62	67.3	297.9	365	0.29	0.04	308	364

\*Hemoglobin concentration (g/dL).

†Weight × 7 mg/kg.

‡Hemoglobin iron, assumes blood volume of 75 mL/kg, and that 1 g hemoglobin contains 3.47 mg iron.

§Sum of tissue iron and hemoglobin iron.

||Total body iron, corrected for estimated iron absorption in exclusively breastfed. Column A represents a conservative estimate of breast milk iron (0.048 mg/kg/d) and iron absorption (20%), while B is more generous (0.075 mg/kg/d and 50% absorption).

¶Assumes iron content at birth is 75 mg/kg.

Data from Moe PJ: Normal red blood picture during the first three years of life. *Acta Paediatr* 54:69-80, 1965 (mean hemoglobin); World Health Organization Working Group on Infant Growth: An Evaluation of Infant Growth. Geneva, Nutrition Unit, World Health Organization, 1994 (weight of breastfed male infants).

months, but small amounts of fruit purée were permitted. Formulas contained 4 to 7 mg/L iron. No significant difference was found in hemoglobin concentration, serum iron, mean cell volume, or serum transferrin receptors between breastfed and formula-fed infants at 6 weeks or 6 months of age.

One small ( $N = 4$ ) observational study<sup>50</sup> suggested that prolonged exclusive breastfeeding (8–18 mo) may be compatible with normal iron nutritional status.<sup>50</sup> A larger study ( $N = 30$ ) showed somewhat different results.<sup>59</sup> Infants received no medicinal iron, iron-fortified milk, or iron-fortified cereals. By 12 months of age, 30% of infants had a hemoglobin concentration of less than 11 g/dL, and 43% had serum ferritin levels of less than 10  $\mu\text{g/L}$ <sup>59</sup>; however, the infants with the low hemoglobin or ferritin values were those who stopped breastfeeding earlier and subsequently were given low-iron formula and non-iron-fortified weaning foods. Infants who continued to breastfeed exclusively had a reduced incidence of anemia.<sup>59</sup> None of the nine infants who were exclusively breastfed longer than 7 months were anemic at 12 months of age. This study therefore suggests that exclusive breastfeeding is compatible with normal iron status; however, after breastfeeding is stopped, iron deficiency is likely if iron-fortified formulas and cereals are not used. The use of non-iron-fortified cereals and formulas after the discontinuation of breastfeeding seems to result in an unacceptably high prevalence of iron deficiency.

In a study of feeding practices after 6 months of age, only 1 of 72 formerly breastfed infants had iron-deficiency anemia at age 6 months (1.4%).<sup>48</sup> An additional 11 infants (15.3%) had iron deficiency and were re-evaluated 6 to 8 weeks later. By then, 2 of 11 had developed iron-deficiency anemia (cumulative prevalence, 4.2%).<sup>48</sup>

Few true, randomized, controlled trials have examined the effect of iron supplementation during breastfeeding. One small study compared the effect of 10 mg per day iron supplementation to term infants compared with placebo.<sup>7</sup> Iron supplementation increased the hemoglobin concentration of some subsets of infants, notably those of lower birth weight, and boys of higher socioeconomic status. This study, however, predated the widespread introduction of iron-fortified foods into the weaning diet. There has been a steady increase in the iron intake of infants since the 1960s.<sup>76</sup>

From these studies, human milk-feeding seems to be adequate to prevent iron-deficiency anemia during the first 6 months of life, and possibly much longer. After 6 months of age, the introduction of iron-fortified cereals may support normal iron status. After exclusive breastfeeding is stopped, iron-fortified formulas and cereals should be introduced. The use of non-iron-fortified formulas and cereals after exclusive breastfeeding increases the risk for iron deficiency.

## PREVENTION OF IRON-DEFICIENCY ANEMIA IN HUMAN MILK-FED INFANTS

Recommendations regarding the prevention of iron-deficiency anemia have been released by the Centers for Disease Control and Prevention.<sup>9</sup> Recommendations for full-term infants also have been made available by the American Academy of Pediatrics<sup>1, 2</sup> and the Canadian Paediatric Society.<sup>14</sup> The authors' recommendations (see subsequent discussion) represent a summary of these reports as relative to human milk-fed infants.

Primary prevention of iron-deficiency anemia in the human milk-fed infants relies on the introduction of iron-fortified weaning foods by approximately 6 months of age. If supplementary milk feeds are required during infancy, they

should be in the form of iron-fortified milk. Cow's milk is best avoided for infants with iron deficiency. Iron-fortified milk is best avoided for infants with iron deficiency. Iron-fortified milk is best avoided for infants with iron deficiency. Iron-fortified milk is best avoided for infants with iron deficiency.

Secondary prevention of iron deficiency in infants between ages 9 and 12 months should be considered. This recommendation is restricted to high-risk population groups, such as those with poor growth, or who did not receive iron supplements because of the anemia should be considered. Iron-fortified milk (< 10  $\mu\text{g/L}$ ) to distinguish iron deficiency anemia, lead poisoning, or rarer causes of anemia.

Preterm and low birth weight infants require current recommendations are that iron supplementation starting at 2 months of age or at home. Iron may be met only in human milk. Iron supplements, such as ferrous sulfate. The requirements in these infants may be met only in human milk. In a study,<sup>35</sup> an iron intake of 1 mg/day in a population of preterm infants who were relatively early and avoided cow's milk was found to be at high risk for iron-deficiency anemia. Further studies are required before these recommendations are generally applied. In this high-risk population, iron-deficiency anemia at 6, 12, and 18 months of age.

## SUMMARY

Given the importance of iron in human development, it is surprising that there are surprisingly few true, randomized, controlled trials. However, it seems that iron deficiency during the first 6 months of life is usually sufficient to meet requirements. At 6 months, iron stores are depleted and become dependent on a diet. Iron deficiency is a significant nutritional problem. The effects of iron deficiency in this age group are similar to those reported in animal studies or studies of iron deficiency in children. Because of the uncertainty of the adverse effects of iron deficiency anemia,<sup>17</sup> currently, the recommendation is to avoid prolonged breastfeeding, avoid iron-fortified formulas and cereals, and the introduction of iron-fortified weaning foods by approximately 6 months of age.

Despite much research, there are still many questions about the supplementation of infants, including:

1. The optimal age for introduction of iron-fortified weaning foods is poorly defined and should be further studied.
2. The natural history of iron deficiency in the first year of life is unclear, especially on development of iron deficiency anemia.
3. The biologic variability among infants allows many infants who do not

permitted. Formulas contained iron in hemoglobin concentration-transferrin receptors between 6 and 12 months of age.

It is suggested that prolonged exclusive breastfeeding is associated with normal iron nutritional status.<sup>50</sup> Inconsistent results.<sup>59</sup> Infants received iron-fortified cereals. By 12 months of age, hemoglobin concentration of less than 11 g/dL, and ferritin concentration < 100 µg/L<sup>59</sup>; however, the infants with iron deficiency who stopped breastfeeding and received iron-fortified formula and non-iron-fortified formula had a reduced iron status. Those who were exclusively breastfed for 6 months of age. This study therefore suggests that iron deficiency is likely if iron-fortified cereals and non-iron-fortified cereals and formula seem to result in an unacceptably low iron status.

At 6 months of age, only 1 of 72 formerly breastfed infants (1.4%).<sup>48</sup> An additional 6 to 8 infants were re-evaluated 6 to 8 months of age and found to have iron deficiency anemia (cumulative prevalence 1.4%).

The study examined the effect of iron supplementation in a study compared the effect of iron supplementation in infants compared with placebo.<sup>7</sup> The study found a concentration of some subsets of iron-fortified formula and boys of higher socioeconomic status had a steady increase in the iron status.

It seems to be adequate to prevent iron deficiency during the first 6 months of life, and possibly much more so if iron-fortified cereals may be introduced when breastfeeding is stopped, iron-fortified formula. The use of non-iron-fortified formula increases the risk for iron deficiency anemia.

## IN HUMAN

Infants with iron deficiency anemia have been studied and Prevention.<sup>9</sup> Recommendations are available by the American Academy of Pediatrics.<sup>14</sup> The authors' report represents a summary of these findings.

In the human milk-fed infants receiving iron-fortified weaning foods by approximately 6 months of age, they found that iron deficiency anemia was not prevented.

should be in the form of iron-fortified formula rather than nonfortified formula. Cow's milk is best avoided for at least the first year of life. The addition of vitamin C-enriched foods or puréed fruits after age 6 months may increase iron bioavailability from the diet and improve iron nutritional status.

Secondary prevention of iron-deficiency anemia involves the screening of infants between ages 9 and 12 months for a low hemoglobin concentration and again at age 18 months. This recommendation may be applied universally or restricted to high-risk populations, such as infants of low birth weight, rapid growth, or who did not receive iron-fortified cereals by 6 months of age. The cause of the anemia should be confirmed by a low serum ferritin concentration (< 10 µg/L) to distinguish iron deficiency from other nutritional causes of anemia, lead poisoning, or rarer causes.

Preterm and low birth weight infants have high iron requirements,<sup>27</sup> and current recommendations are that they receive at least 2 mg/kg per day iron starting at 2 months of age or at hospital discharge.<sup>3,27,28</sup> These high requirements may be met only in human milk-fed, preterm infants with medicinal iron drops, such as ferrous sulfate. There is some suggestion, however, that the iron requirements in these infants may be less than previously thought. In one study,<sup>35</sup> an iron intake of 1 mg/kg per day prevented iron deficiency in a population of preterm infants who were started on iron-fortified weaning foods relatively early and avoided cow's milk during the first year of life. Given the high risk for iron-deficiency anemia in preterm infants, however, additional studies are required before these lower levels of supplementation may be universally applied. In this high-risk population it also may be prudent to screen for iron-deficiency anemia at 6, 12, and 18 months of age.

## SUMMARY

Given the importance of iron nutrition during the first year of life, there are surprisingly few true, randomized, controlled studies addressing this issue; however, it seems that iron deficiency is unlikely in full-term, breastfed infants during the first 6 months of life<sup>19</sup> because these infants' body iron stores are sufficient to meet requirements. After this time, many infants exhaust their iron stores and become dependent on a secondary dietary iron supply. Although iron deficiency is a significant nutritional problem worldwide, most of the adverse effects of iron deficiency in this age group are hypothetical and rely on extrapolation from animal studies or studies at different ages. This, however, also is true of most of the adverse effects of iron excess in this age group. Given this uncertainty, it seems prudent to use the lowest dose of iron that prevents iron-deficiency anemia.<sup>17</sup> Currently, the best evidence is that this is achieved by prolonged breastfeeding, avoidance of unfortified formulas and cow's milk, and the introduction of iron-fortified and vitamin C-fortified weaning foods at approximately 6 months of age.

Despite much research, there are many areas of uncertainty regarding iron supplementation of infants, including that:

1. The optimal age for introducing iron-fortified supplemental foods is poorly defined and should be further evaluated.
2. The natural history of iron deficiency and iron-deficiency anemia during the first year of life is unclear, as are the possible long-term effects of this, especially on developmental outcome.
3. The biologic variability among infants and among their mothers that allows many infants who do not receive iron-fortified foods to prevent iron deficiency anemia.

iron deficiency while receiving only human milk throughout the first year of life is intriguing and warrants additional study.

4. The iron requirements of small-for-gestational-age, term infants are unknown. Their iron requirements are likely to be higher than those of average term infants, but whether iron supplements are required is unclear.
5. The optimum amount of dietary iron in the weaning diet needs to be further defined. Similarly, the optimal source and amount of iron in infant formulas given to infants who receive a mixture of human milk and formula is unclear.

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