Balancing Benefits and Risks of Iron Fortification in Resource-Rich Countries

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For the last 25 years, the American Academy of Pediatrics (AAP) has endorsed the use of iron-fortified infant formulas, noting "no role for the use of low-iron formulas." The rationale for these policies was the recognition that the increase in the use of iron-fortified formulas, accounting for 80% of all formula sold in 1985, was responsible for the declining prevalence of iron-deficiency anemia in US infants.[1] These recommendations were also based on the absence of evidence of discernible adverse effects. Controlled trials had reported no differences in gastrointestinal symptoms, such as colic, constipation, diarrhea, regurgitation, and fussiness, among infants receiving low-iron vs iron-fortified formulas.[2,3] Likewise, evidence was lacking to support another theoretical concern of clinically significant interactions with other micronutrients, specifically zinc and copper. In 1999, the AAP took an even stronger stand and recommended that low iron formulas be removed from the market entirely,[4] for reasons similar to those of the 1989 policy. Further, it was recommended that the minimum iron content for all term infant formulas be at least 4 mg/L.[4] Currently, standard, term infant formulas on the market are all iron-fortified and contain 4-12 mg/L of iron, even though there are some regional differences. In the US, the AAP recommends that infant formulas have an iron content of 10-12 mg/L[5]; in Europe, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends 4-8 mg/L.[6]

In the recommendations, the contrast in the iron exposure of formula-fed infants vs breastfed infants has primarily focused on the better bioavailability of the iron in breast milk. Although an absorption efficiency of approximately 50% is often quoted, some studies have actually reported absorption in the range of 12%-16%,[7,8] making that bioavailability distinction much less potent. This also suggests that absorption of substantial amounts of dietary iron simply is not critical during the early months of life in healthy infants of normal birth weight. Among all the compositional differences between human milk and formula, the differences in iron content are the most extreme. Virtually all mammalian milks are low in iron, with the exception of rodents, in which postnatal growth is extremely rapid. It seems implausible that this conserved biological pattern is without purpose. It is also clear that iron deficiency occurs in breastfed infants only after the very early months of life. The practical challenge is to identify when the birth iron endowment is exhausted, at which point the infant needs a source of iron from the diet.

This article will discuss the potential advantages of a low iron intake for the infant and the potential adverse effects of drastically altering this, especially in the first 6 months of life. From the outset, two realities must be acknowledged. First, iron deficiency (especially without anemia) in infants remains common, particularly in high-risk groups, including older normal breastfed infants and premature and/or in low birth weight infants. Whether this mild iron deficiency has adverse effects on development is not known. Second, research on potential adverse effects of early and excessive iron exposure is limited, and the evidence base for caution is suggestive but not yet demonstrated by rigorously designed trials. Thus, this represents an emerging area of consideration, and, given the advances in understanding of iron metabolism, the interaction between iron and inflammation, and the importance of early influences on the immature gut and immune system, it is an area that warrants much stronger scientific investigation.

Mineral Concentrations in Human Milk vs Formula

The iron concentration in early human milk is ~0.5 mg/L and declines slightly to ~0.2-0.4 mg/L in mature milk.[9] Thus, even with a relatively low level of fortification in infant formula (eg, 4 mg/L), the amount is ~10-fold higher. For the high end of fortification levels (eg, 12 mg/L), the difference is up to 60-fold greater. Thus, typical intakes from formula by the young infant represent a distinctly unnatural exposure. Another distortion of the balance of micronutrients resulting from fortification of formula is the ratio of zinc to iron. In contrast to iron, zinc is very high in early human milk (2-3 mg/L) and remains >1 mg/L until ~6 months postpartum.[10] Therefore, during the 0- to 6-month period, the Zn:Fe in human milk is ~3-8, depending on the stage postpartum (or Fe:Zn ~0.25). In contrast, current levels

AAP	American Academy of Pediatrics
T1DM	Type 1 diabetes mellitus

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of iron and zinc fortification in formulas are the opposite; the iron concentration is typically about twice that of zinc, which is at least 5-7 mg/L, resulting in Zn:Fe of only 0.5. The effects of this difference are unknown but may be relevant to the effects discussed below.

Potential Adverse Effects of High Iron Exposure in Early Life

Inflammatory and Oxidative Stress Responses

Iron is recognized as a reactive element; its easy redox cycling properties contribute to its utility as a biocatalyst in proteins and as an electron carrier in energy metabolism. It is, however, a potent pro-oxidant. Under anoxic or anaerobic conditions, free iron can be toxic by the formation of reactive oxygen species, including superoxide and other free radicals. Thus, given the "double-edged sword" features of iron—its essentiality as a nutrient and its potential toxicity—very little free iron is present in the circulation under normal circumstances. The majority of iron is bound as part of the heme molecule in hemoglobin; the other major pool is storage iron in the form of ferritin. During transport in the circulation, iron is tightly bound to transferrin.

Growth

Additional iron given to iron-replete infants has been suggested to impair growth. This has been shown in several randomized, controlled studies where iron supplementation was given to infants after 4 months of age.[11-14] However, this possible adverse effect has not been confirmed in meta-analyses.[15] Only a few studies have compared growth of infants <4 months of age receiving formulas with different levels of iron fortification. One small study compared 2 vs 4 mg/L and found no difference in growth between the 2 iron levels or any difference between the formula-fed and breastfed infants from 1-6 months of age.[16] An earlier randomized trial compared two relatively high iron concentrations (7.4 vs 12.7 mg/L formula) from 1-6 months and found no difference between the two groups, but both groups were longer and heavier than a concurrent group of breastfed infants.[17]

Mineral-Mineral Interactions

Potential interactions among trace minerals were noted in the 1989 AAP policy statement and are often raised as a concern for adverse effects of iron fortification and supplementation.[18-20] Several investigations have been undertaken to evaluate this, and, overall, the evidence does not support a potent adverse effect of iron fortification on either zinc or copper absorption.[21-23] Several investigators have shown that iron supplements decrease serum or plasma zinc concentrations.[19,20,24,25] However, plasma zinc, as an index of zinc status, has low sensitivity, is susceptible to many confounding factors including inflammation, and is not a direct reflection of absorption. Data on the effects of different levels of iron fortification in formula have been somewhat conflicting, with very high iron fortification (~14-19 mg/L vs 1.4-2.4 mg/L) having a depressing effect on plasma zinc concentrations in 3- to 4-month-old infants.[26]

Infections and Gastrointestinal Problems

A frequently cited systematic review of oral iron supplementation trials reported a modest but statistically significant increase in the risk of developing diarrhea with oral iron administration, but this review was not specific for or limited to fortification of formula nor to young infants.[27] Recent trials in Pakistan, Ghana, and Kenya[28-30] relating iron-containing micronutrient powders to increased diarrhea, including severe and bloody diarrhea, also are not within the scope of this chapter, which concerns infants in resource-rich countries.

As noted above, the early recommendations for the safety of iron-fortified formulas, including from birth, were based on trials undertaken with different levels of fortification.[2,3] Gastrointestinal complaints such as constipation, spitting-up, vomiting, fussiness, or cramping were not different among infants randomized at birth and continued on fortified (12 mg/L) or unfortified (1.5 mg/L) formulas for approximately 6-12 weeks.[2,3] Both studies concluded that, in the absence of gastrointestinal signs or symptoms, "there are few indications for feeding commercially prepared formulas that are not fortified with iron."[2]

Relevant to the topic of this article, the gastrointestinal tract of the young infant is particularly vulnerable to any imbalances that can alter the mucosal barrier function, the maturation of the intraepithelial tight junctions and intestinal permeability, and the development of the innate immune system and a favorable intestinal microbial community. In recent years, there has been a growing appreciation of the critical interrelationships of the enteric microbiome with the host immune system and metabolism and of the influence of diet on both the compositional and functional features. In particular, early postnatal life is a time for intestinal maturation and colonization by the commensal microbiota and the establishment of immunologic and metabolic programming that may have long-term consequences. Differences in the enteric microbiome between breastfed and formula-fed infants have been clearly documented.[31-33] Generally recognized patterns include breastfed infants as having higher counts of *Bifidobacteria* and *Lactobacillus* and lower counts of *Bacteroides*, *Clostridium coccoides* group, *Staphylococcus*, and *Enterobacteriaceae* than formula-fed infants.[34] Breast milk is an important source of the specific colonization pattern of the infant that resembles closely the maternal genotypes. Prebiotics, especially human milk oligosaccharides, are thought to favorably shape the commensal bacteria of the newborn's intestinal tract. In addition to feeding type, mode of delivery, antibiotic exposure, and environmental factors have been found to influence the enteric microbiome.[34] However, primary determinants of its composition within different nutritional sources are not yet clear.

The potential impact of iron exposure on young infants' microbiota has not been investigated in controlled interventional studies. Interest is emerging specifically on the