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Review

Too Much of a Good Thing: Evolutionary Perspectives on Infant Formula Fortification in the United States and Its Effects on Infant Health

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ABSTRACT: Recently, there has been considerable debate regarding the appropriate amount of iron fortification for commercial infant formula. Globally, there is considerable variation in formula iron content, from 4 to 12 mg iron/L. However, how much fortification is necessary is unclear. Human milk is low in iron (0.2–0.5 mg/L), with the majority of infant iron stores accumulated during gestation. Over the first few months of life, these stores are depleted in breastfeeding infants. This decline has been previously largely perceived as pathological; it may be instead an adaptive mechanism to minimize iron availability to pathogens coinciding with complementary feeding. Many of the pathogens involved in infantile illnesses require iron for growth and replication. By reducing infant iron stores at the onset of complementary feeding, infant physiology may limit its availability to these pathogens, decreasing frequency and severity of infection. This adaptive strategy for iron regulation during development is undermined by the excess dietary iron commonly found in infant formula, both the iron that can be incorporated into the body and the excess iron that will be excreted in feces. Some of this excess iron may promote the growth of pathogenic, iron requiring bacteria disrupting synergistic microflora commonly found in breastfed infants. Evolutionarily, mothers who produced milk with less iron and infants who had decreased iron stores at the time of weaning may have been more likely to survive the transition to solid foods by having limited iron available for pathogens. Contemporary fortification practices may undermine these adaptive mechanisms and increase infant illness risk. Am. J. Hum. Biol. 26:10–17, 2014. © 2013 Wiley Periodicals, Inc.

Breastfeeding is well established as an important determinant of infant morbidity and mortality. This is particularly true for infants in low resource, highly pathogenic environments where breastfeeding is protective against illness (Arifeen et al., 2001; Golding et al., 1997; Ip et al., 2007), though the differences persists in high resource, low pathogen environments such as the United States (Ball and Wright, 1999; Bartick and Reinhold, 2010; Scariati et al., 1997).

These discrepancies in morbidity and mortality between breastfed and formula fed infants have been long assumed to reflect decreased immunological contributions from human milk (Oddy, 2001). The immunological factors in human milk include secretory immunoglobulin A, a broad-spectrum mucosa-specific immunoglobulin, bactericides such as lysozyme, cytokines (Brandtzaeg, 2003; Hanson and Korotkova, 2002; Stepans et al., 2006), and oligosaccharides (Donovan et al., 2012; German et al., 2008). Recent evidence suggests that not only is milk rich in immunologically supportive factors and nutrients, it is also capable of rapid responsiveness through the increase of leukocytes and immune factors to maternal or infant infection (Hassiotou et al., 2013; Riskin et al., 2012). While the absence of immunological factors from breast milk has long been hypothesized as the reason for increased illness frequency in formula fed infants, this absence may not be the only risk of formula feeding. The iron in infant formula may be an additional risk factor for neonatal infection.

It has been previously proposed that differences in dietary iron intakes between breastfed and formula fed infants may contribute to the increased morbidity of formula-fed infants (Domellöf, 2007; Faldella et al., 2003; Moy, 2000). Iron is well known for its role in infectious diseases etiology (Bullen et al., 1991), and is found in significantly greater quantities in infant formula than human milk. An essential micronutrient for infant growth and development, iron is also necessary for the growth and replication of many pathogenic bacteria. In adults, elevated dietary iron or systemic iron is a risk factor for infection and similar risks are likely in children and infants (Gera and Sachdev, 2002; Ward et al., 1996). However, missing from these prior studies is an evolutionary context that provides a framework for understanding why low levels of iron evolved in human milk and how these low levels may contribute to iron handling in the neonate.

Building on prior work showing the links between dietary iron and infection in adults, Wander et al., (2009) have proposed that principles of evolutionary medicine can be successfully applied to understanding iron and pathogen associations for children living in highly pathogenic environments. They report that decreased systemic iron (deficiency but not anemia) among 5–10 year old children reduces the risk of infection and may be both a behavioral and a biological strategy for minimizing infection. Infants however, are missing from this discourse but the model actually fits quite well. Infants, unlike children or adults, will shift from a comparatively low risk food—human milk—to complementary foods and their increased risk of contamination. Comparatively immunologically naïve, infants are at increased risk of contracting novel infections. Reducing iron stores during the early infancy may be protective against contracting an infection and, should one be contracted, may also limit the severity.

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These associations have been reported elsewhere, including the suggestion that decreased iron transfer—and lower levels of systemic iron—may be normal during infancy. Other factors in human milk contributing to iron regulation may also work at the level of the microbiome (Vael and Desager, 2009), possibly contributing to differences in bacterial composition around the time of complementary feeding. Framing natural declines in infant iron stores as an adaptation for immune protection, rather than as a pathology (Ryan, 1997), may provide insights into appropriate fortification practices for commercial infant formula and even supplementation recommendations of breastfed infants that are in line with this adaptation, rather than mismatched to neonatal needs.

Consistent with the immunological advantage observed in older children, evolutionarily, infants with lower bodily iron stores at weaning may have been less likely to die of infections, providing positive selection for reduced bodily iron stores. Contemporary infant feeding practices, specifically the use of heavily iron fortified infant formula, interferes with this normal physiological decline. It may be that this continued accumulation of iron and the ready availability of iron in infant formula during digestion contribute to the increased risks of infection found among formula fed infants. This association between current fortification practices and infant risk suggests the following hypotheses: (1) Human milk (and primate milk more broadly) is low in iron as an evolutionary adaptation to minimize iron availability to pathogens during weaning; and (2) Current fortification practices for commercial infant formula in the United States are mismatched to this adaptation and contain an excess of iron.

COMMON PRACTICES OF COMMERCIAL FORMULA IRON FORTIFICATION AND POSSIBLE HEALTH EFFECTS

As primates, dietary iron excess would have been extremely rare throughout most of human evolutionary history. Rhesus macaque milk contains 1.76–1.18 μg/mL; similar data for other primate species are largely unavailable (Lönnerdal et al., 1984). Given that milk was the primary source of nutrients for infants during most of human evolution, infant iron sources initially would have been initially limited to iron accumulated prior to/just after birth or derived from mother's milk. Iron concentrations in human milk start relatively low (∼0.6 mg/L) and decline from birth to 5–6 months when they plateau around 0.2–0.3 mg/L, at least in the few populations studied thus far (Dorea, 2000; Feeley et al., 1983; Siimes et al., 1979). About 15–42% of the iron in human milk is bioavailable (Domellöf et al., 2002b; Hicks et al., 2006). Interestingly, there is minimal evidence for an association between milk iron content and maternal iron status (Nakamori et al., 2009; Yalcin et al., 2009), except in cases of severe maternal anemia and then only for transitional milk (Kumar et al., 2008); there was no association between maternal hemoglobin and milk iron in mothers with mild or moderate anemia in either the Indian population studied by Kumar et al., or in similar study done in Brazil (França et al., 2013). This general independence of milk iron from maternal hemoglobin suggests active, rather than passive transfer of iron into maternal milk as passive transfer should generally be in proportion to maternal iron status. However, in mothers with severe anemia, milk iron may be compromised.

Dewey (2004) has proposed that mothers may be able to replete iron stores during lactation provided maternal diets are adequate in iron. Closely spaced pregnancies may limit this capacity for recovery (Miller, 2010). Kalkwarf and Harrast (1998) reported upregulation of iron absorption in lactating women. Increased capacity for absorption may facilitate recovery of maternal iron stores and may contribute to the typical independence of milk iron from maternal iron. Alternatively, the decrease in milk iron in later lactation may be an additional mechanism for maximizing iron availability for future pregnancies, as the iron requirements of gestation can be significant.

Iron fortification of infant formula is significantly greater than the iron content of human milk. However, while the majority of milk iron is thought to be bioavailable to the infant, only a small portion of formula iron is, and as such, significantly greater quantities of iron are necessary to ensure appropriate intake. Formula bioavailability is estimated at 7–14% (Nutrition, 1999; Saarinen and Siimes, 1977).

Infant formula fortification guidelines differ by county. Most commercial European infant formulas subscribe to the ESPGHAN Global Standards and contain 4–8 mg/L of iron (Koletzko et al., 2005), as recommended by the ESPGHAN expert panel. By comparison, although the United States participated in the ESPGHAN international expert panel, fortification recommendations remain unchanged. US formula is typically fortified with 10–12 mg/L of iron, significantly more than recommended by the Global Standards. The general suggestion is that this is necessary to prevent IDA, although the evidence presented by ESPGHAN demonstrated that lower levels of fortification are equally effective and elevated levels of fortification may be harmful (Lozoff et al., 2012).

To compare, approximate estimates of daily infant intakes, both fortification and absorption rates can be estimated for an "average" male infant (Fig. 1). This average male infant would grow on the fiftieth centile for both weight and length, consuming the recommended daily volume of formula or equivalent amount of human milk for weight across the first year of life (Fig. 1). The iron content of human milk is set at 0.47 mg/L (Dorea, 2000) with an absorption rate of 29.15%, the average from two prior studies (Domellöf et al., 2002b; Hicks et al., 2006). Formula iron is set at three different fortification levels commonly found in the United States and Europe: 4, 7, and 12 mg/L formula iron absorption is set at 7% (Saarinen and Siimes, 1977). The estimates shown in Figure 1 demonstrate considerable differences in daily iron intake. Despite lower rates of absorption, total absorbed iron is higher under all formula exposures compared with human milk fed infants. Iron absorption rates from formula may be even higher, for the purposes of illustration, only the lowest rate reported in the literature was used. The intake of iron at 12 mg/L is much greater than the estimated requirements of the infants as illustrated. While infants undoubtedly need iron, these requirements are meet easily at 8 mg/L and the fortification practices of US formula appear excessive compared with breast milk, lower iron formula, and infant needs.

Increased iron fortification poses two different potential risks for infants. The first risk is iron overload, whereby excess iron is absorbed by the infant and accumulates in tissues possibly leading to damage. The second risk is the presence of unused iron in the intestines. While most of

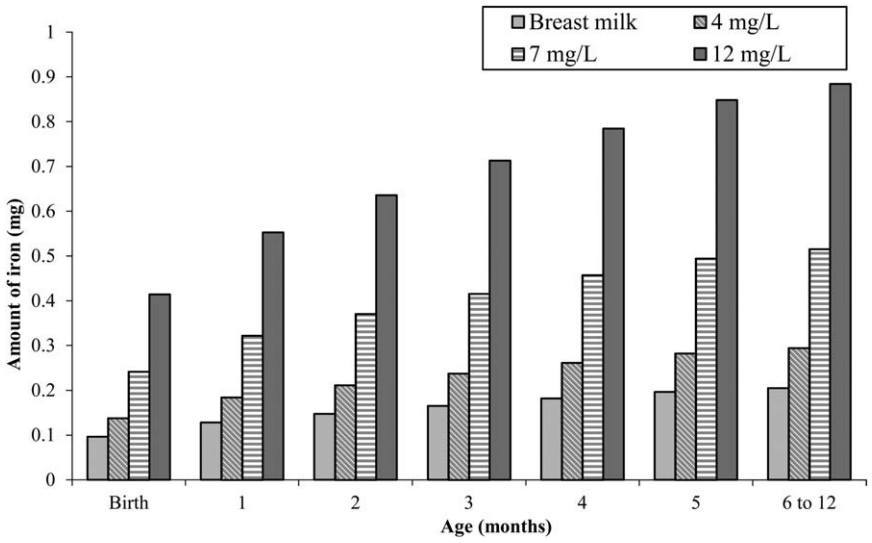

Fig. 1. Estimated daily intake of iron by a male infant across the first year of life, consuming breast milk, infant formula containing 4 mg/L of iron, 7 mg/L of iron, and 12 mg/L of iron; assuming 9% of the iron in formula and 50% of the iron in breast milk is absorbed. Estimated daily intake was calculated using the CDC fiftieth percentile of weight for age and corresponding recommended daily intake in ounces of formula or human milk.

this iron will be lost in feces, it does provide a potential iron source for pathogenic iron-requiring bacteria in the intestines, and this may contribute to the differences in the composition of the infant intestinal microbiome between breastfed and formula fed infants (Balmer and Wharton, 1991; Chierici et al., 2003; Marques et al., 2010).

IRON REGULATION IN INFANCY

The amount of iron that the human body requires is unknown, especially for infants, and appears highly variable both between individuals and across developmental stages. These requirements not only change over the course of infancy, but so does the portioning of iron within the body (Domellöf et al., 2002a; Faldella et al., 2003). Infants have approximately 300 mg of systemic iron, with 240 mg in use by erythrocytes and the remainder maintained in the spleen, liver, bone marrow, and other tissues (Domellöf, 2007). Iron absorption takes place primarily in the duodenum and upper jejunum of the small intestines. The amount of iron absorbed is responsive to dietary cofactors and current iron status (Domellöf et al., 2002b). Although iron absorption does decrease when iron stores are plentiful, it does not cease completely. This is particularly true for infants who have underdeveloped iron uptake regulatory mechanisms and may continue to absorb considerable quantities of iron despite sufficient iron stores (Lönnerdal and Kelleher, 2007), increasing the potential for iron overload.

Infant iron requirements are poorly understood. In a cross sectional study of unsupplemented infants compared to supplemented infants, (Domellöf et al., 2002a) reported differences in the distribution of iron status. Unsupplemented infants had normal distribution of hemoglobin, whereas supplemented infants had a skewed distribution.

Three primary proteins are involved in iron regulation: ferritin, transferrin, and lactoferrin. Ferritin stores iron ions and functions primarily as an intracellular reservoir. Iron transport between tissues relies on transferrin and lactoferrin, each with tissue-specific functions. Transferrin is mainly found in serum, while lactoferrin is the iron transport molecule of the mucosa and milk and maintains structural integrity in acidic environments. In neonates, lactoferrin is believed to play a primary role in regulating iron uptake (Davidson and Lönnerdal, 1987; Domellöf, 2007; Suzuki et al., 2005) both enhancing and down-regulating intestinal iron absorption prior to the maturation of other iron regulatory systems (Davidsson et al., 1994; Fairweather-Tait et al., 1987).

Human infants are not born with the ability to synthesize lactoferrin (Goldman et al., 1990). Colostrum—the milk produced in the first few days after delivery—contains large amounts of lactoferrin, and overall production of lactoferrin increases during the first few weeks as milk volume increases resulting in an average concentration of 2–4 g/L of lactoferrin in mature human milk (Lien et al., 2004; Shashiraj et al., 2006).

In addition to its role in iron regulation, lactoferrin is also a key component of the mucosal immune system and has broad spectrum antifungal, antibacterial, and antiviral properties specifically related to whether or not it is currently binding iron ions (Conneely, 2001; Legrand et al., 2004). Iron-binding lactoferrin is known as hololactoferrin while unbound lactoferrin is known as apolactoferrin. Iron sequestration by apolactoferrin, converting it to hololactoferrin, is a basic immunological strategy for limiting pathogen growth. First, it limits iron available to pathogens (Valenti et al., 2004). Secondly, apolactoferrin can actively fight infection, binding to lipopolysaccharides (LPS) on bacteria cell membranes and blocking LPS-mediated cytokine release while also increasing cell membrane permeability, facilitating detection and destruction of the cell by the immune system (Legrand et al., 2004; Oria et al., 1988).

IRON REGULATION OF GUT MICROFLORA

Iron availability in the intestines also appears to influence the composition of the microflora. Breastfed infants

typically have microflora characterized by high levels of the iron independent *Lactobacillus* and *Bifidobacterium* (Bezirtzoglou et al., 2011; Grönlund et al., 2007; Kleessen et al., 1995), while formula fed infants have higher levels of *Escheria*, *Enterococci*, and *Clostridia* (Chierici et al., 2003; Dai and Walker, 1999; Penders et al., 2006; Rubaltelli et al., 1998). Balmer and Wharton (1991) have proposed that the excess iron in infant formula may explain these differences in microflora. In breastfed infants, free iron concentrations in the gut are likely very low, and cannot support large colonies of iron-requiring pathogenic bacteria. However, given that only 7–14% of iron in formula is bioavailable to the infant, the remaining 86–93% of iron (6.5–11.7 mg/L) will be present in the intestines anyways, at least until fecal excretion (Hyams et al., 1995). Decreased iron absorption in the intestines likely enhances its availability to iron-requiring, often pathogenic bacteria. Overgrowth of these bacteria may alter the pH of the intestines, further promoting pathogenic bacterial growth (Collado et al., 2012). Large amounts of unbound gastrointestinal iron would be evolutionarily novel, and may contribute to the differences in intestinal microflora as previously described. In focusing only on the iron that is absorbed by the infant, the possible effects of the additional iron on the infant microbiome are largely overlooked. This suggestion has not been previously proposed that the iron not absorbed may as an important in influencing infant health as the iron that is absorbed.

Changes in the microflora of the intestines may further compromise the innate immune response to infection, especially to pathogenic *E. coli*. Usually, *Lactobacillus* and *Bifidobacterium* competitively inhibit growth of *E. coli* and similar bacteria by binding to specific cellular receptors and interfere with the attachment mechanism of many pathogenic strains of bacteria (Duffy, 2000; Kim et al., 2008). *Lactobacillus* and *Bifidobacterium* also contribute to localized immunological response (West et al., 2012) by themselves producing chemokines, which attract systemic immune factors (Wells, 2011).

Overall, it appears that current commercial infant formula fortification practices may result in an excess of dietary iron with possible consequences to the composition of the infant intestinal microbiota and long term health. The typical flora of breastfed infants, *Lactobacillus* and *Bifidobacterium*, are iron independent bacteria, further highlighting the evolutionary novelty of excess dietary iron during infancy.

Recently, Krebs et al., (2013) have reported changes in infant microflora associated with different iron intakes during weaning. Exclusively breastfed infants were randomized to iron-fortified cereal, iron and zinc fortified cereal, and meat. In the groups receiving iron fortified cereal, there was a decline in both Firmicutes and Actinobacteria, the phylas containing *Lactobacillus* and *Bifidobacteria* respectively; these declines were not present in the meat or iron and zinc fortified groups. The dietary shift associated with the transition from human milk to family foods fundamentally alters the composition of the intestinal microbiota (Thompson, 2012) in both breastfed and formula fed infants, and likely driven primarily by the differences in macronutrients and oligosaccharides between human milk and commercial infant formula. Some of the shift may be related to changes in iron availability as originally hypothesized by Balmer and Wharton (1991), and seen in older infants and children with the addition of iron fortified biscuits as an IDA preventive treatment (Zimmermann et al., 2010). However, specific studies looking at differences in the microbiome between infants randomized to formula with different amounts of iron have not been conducted so direct comparisons are impossible at present.

THE IMPRINT OF EVOLUTION: DEVELOPMENTAL CHANGES IN IRON METABOLISM AND LACTOFERRIN DURING HUMAN INFANCY

Although the amount of iron in human milk is relatively limited compared with formula fortification, it is likely that infant iron requirements can be meet by human milk iron in most circumstances. This may not be true for premature infants who have had less time to accumulate prenatal iron stores (Long et al., 2012) and may be reduced in infants with early cord clamping (Andersson et al., 2011; Chaparro et al., 2006). Delayed cord clamping is generally associated with increased infant iron stores in early infancy. As the iron in human milk cannot fully meet the infant's metabolic requirements for iron during the first six months of life, iron stores accumulated during gestation, are gradually depleted to meet infant needs. The quantity of stored iron increases with delayed cord clamping (Andersson et al., 2011) providing an important source of metabolic iron.

The critical role of iron in infant development suggests selection on iron delivery through milk, particularly favoring low iron intake by infants during the period of exclusive breastfeeding. The possible deleterious effects of iron accumulation on intestinal pathogens and immune responses suggest that this decline in iron status might not be pathologic, but an adaptive strategy timed to match the most likely ages of encountering novel iron-requiring pathogens. Natural selection has operated on the components of human milk (Goldman et al., 1998), and given its critical role in both human and bacterial growth, it is highly likely that the iron availability in milk has been under selection (Fomon, 1986). Decreased systemic iron during the period of weaning, but not iron-deficiency anemia, may be associated with lower rates of infection or improved survivorship, providing an increase in fitness among infants consuming low iron milk.

Selective pressures on milk iron content may vary between populations; however, there is virtually no comparative data on human milk iron from which to test this hypothesis. Low iron content appears to be the norm for human milk, with human milk iron approximately half that of the iron content of macaque milk. Some of this may reflect differences in growth rates between the two species, as larger bodied humans are much slower growers and may have reduced iron demands for growth. Alternatively, there may have been distinct ecological pressures on human milk iron content. If low levels of iron at the time when complementary foods are introduced were beneficial, changing practices of infant feeding—specifically early use of these foods—may have been a major selective pressure. Elsewhere, the weanling's dilemma has been well described (McDade and Worthman, 1998), and the archaeological record contains numerous examples of deaths occurring around the time of weaning (Turner et al., 2007; Wright and Schwarcz, 1998). Exposure to pathogens, either through food or increased interactions with the environment as

independent motor skills developed, occurs at this age (Wiley and Pike, 1998) in all populations, although there may be considerable variation in the degree of exposure. The transition to agriculture, along with the domestication of animals and the occupation of spaces for extended durations likely increased pathogen exposure of both adults and children. Individuals who had reduced milk iron—or alternatively, who as children were less likely to accumulate iron stores—may have been more likely to survive infancy and would pass these genes on to their own offspring. Low iron, and the decline in bodily stores during infancy, may have been an adaptive strategy for minimizing infections. Human milk, in general but in particular for iron, may be part of the evolved flexibility of human adaptation. Sellen (2007) has argued that complementary feeding is part of this flexibility, and adaptation through milk by natural selection may be an equally important part of human adaptation and the widespread geographical success of human populations.

As a practical matter, this adaptive-strategy view of infant iron intake has significant implications for current feeding practices. Current levels of iron fortification in infant formula, while driven by the perfectly rational goal of trying to minimize the risk of iron-deficiency anemia in infants, may be undermining an adaptive strategy and actually result in more harm than help. Fortification levels are already out of pace with current US recommendations of 0.27 mg/day for infants less than six months of age; the typical formula-fed infant consumes considerably more iron than USDA recommendations.

EVIDENCE THAT LOWER LEVELS OF IRON FORTIFICATION IN FORMULA ARE SAFE

Recent studies provide evidence that decreased dietary iron intakes may be beneficial to infants without increasing the risk of developing iron deficiency anemia. Among infants in Honduras and Sweden randomized to different concentrations of iron supplementation, the infants with reduced iron intake had lower rates of infection and greater head growth than supplemented peers (Domellöf et al., 2001). Greater iron supplementation did not decrease the already low prevalence of anemia in this sample. It did, however, increase the number of gastrointestinal illnesses and reduce the linear growth of nonanemic children in this same group.

In a US based randomized control trial, Fomon et al. (1997) reported no difference in iron incorporation by erythrocytes between infants receiving formula containing 12 or 8 mg/L. Following a similar study design in Chile, Walter et al., reported no increased risk of iron-deficiency anemia in infants receiving formula fortified with 2.3 mg/L of iron compared to those consuming formula with 12 mg/L of iron (Walter et al., 1998). This low level of formula fortification, currently below infant nutritional guidelines, has also been tested in a handful of other studies. Among infants younger than six months, formula concentrations of 2 and 4 mg/L of iron were sufficient to meet infant needs and prevent iron deficiency anemia (Hernell and Lonnerdal, 2002). A randomized control trial in South Wales, using formula fortified with 1 or 5 mg/L of iron also reported no significant difference in risk of anemia between the two groups of young infants (Tuthill et al., 2002).

In addition to the above studies, a natural trial of iron fortification—that of formula supplementation of 7 mg/L in Western Europe—has not found significantly different rates of anemia when compared with formula fed infants in the United States (Male et al., 2001; Thorsdottir et al., 2003). Elsewhere, it has been suggested that the absence of a difference in risk of iron deficiency anemia between infants fed low iron and standard iron formula should be interpreted as evidence that US standard (12 mg/L) fortification is not harmful to infants (Singhal et al., 2000). However, the differences in infection rates and suggest that more is not necessarily better, more may be worse for infant health.

The trials described previously reported minimal incidence of iron deficiency anemia and in some cases, a reduction in the risk of gastrointestinal illnesses that may be promoted by excess iron. These results are consistent with the overall concept suggested in this article—that human milk has been subject to strong evolutionary adaptive pressure to ensure low unused iron availability to pathogens (especially in the digestive tract) by the time infants are first introduced to increased levels of those pathogens through complementary foods.

LIMITATIONS AND TRADE-OFFS

Iron deficiency anemia is a global public health problem, affecting millions of reproductive aged women, with children at particular risk. Eliminating supplemental iron from infant formula would be tremendously problematic, as iron is a necessary nutrient for normal growth and development. However, in the attempt to minimize the risk of IDA in infants, current fortification practices, especially in the United States, may have gone to excess. Anemia rates are not significantly different between the United States and Western Europe and this has been too often interpreted as a confirmation that more iron is necessary better, instead of asking if 8 mg/L is sufficient, why the additional 4 mg/L would be necessary. More recent evidence suggests that in iron replete infants high doses of iron from formula or supplements may be associated with decreased cognitive function at age 10 (Lozoff et al., 2012). It is likely that iron requirements vary considerably by population, especially with variations in population disease ecology, growth rates, and even placental management. In a high resource, low pathogen environment like the United States, 12 mg/L may be too much of a good thing, as iron requirements may be comparatively low compared with those of children in low resource, highly pathogenic environments were frequent infections may be common. The majority of commercial weaning foods in the United States are also heavily fortified with iron, again to prevent IDA. In other contexts, weaning foods may be modified portions of the adult diet, and may be low iron, especially unfortified cereals. While evolutionarily human infants likely consumed a wide variety of weaning foods depending on ecological variation in available foods, consumption of cereal grains in agricultural communities is well supported by stable isotope studies (Gregoricka and Sheridan, 2012; Turner et al., 2007), while it is thought that foraging populations may have used more variable, and iron rich, weaning foods based on studies of contemporary foraging groups derived primarily from family foods (Fouts, 2004; Gray, 1996; Sellen, 2007; Sellen and Smay, 2001). The increase in grain consumption and potential for pathogen exposure may have provided additional selective pressure favoring lower iron

stores in infancy and minimizing selection on the iron content of human milk. It is likely that excess dietary iron was quite rare, and the fortification levels commonly used in the United States may overwhelm a system adapted to limited iron, and balancing iron requirements of growth against the risk of providing a ready source of iron to pathogens. However, as recent publications attest, the emphasis remains on maximizing iron intake with recent suggestions in Pediatrics by the AAP Section on Nutrition for universal iron supplementation of breastfed infants (Baker et al., 2010), although this has been challenged by the AAP Section on Breastfeeding and several prominent researchers (Breastfeeding et al. 2011; Furman, 2011; Hernell and Lönnerdal, 2011).

Moreover, the long term consequences of iron overload are only beginning to be understood. While the long term developmental, cognitive, and physiological limitations of IDA have been extensively discussed and are certainly very real public health concerns, the consequences of iron overload may also be severe, especially in well-nourished populations with limited iron-depleting infections or parasites. Iron accumulation in neural tissues is thought to play a role in the development of Parkinson's Disease (Youdim et al., 1991), may contribute to specific pathologies within Alhezimer's (Castellani et al., 2007), and may be associated with increased risk of the development of the metabolic syndrome (Psyrogiannis et al., 2003). In children, exposure to high levels of dietary iron by iron replete infants and children is associated with decreased linear growth (Dewey et al., 2002)—but see also Gahagan (2009)—decreased cognitive performance (Lozoff et al., 2012), and altered immune function (Wander et al., 2009). In trying to prevent IDA, high levels of iron fortification of infant formula, particularly at the levels used in the United States when compared to Europe, may be creating additional health consequences for infants.

CONCLUSION

This review is not the first to suggest that current levels of iron fortification in infant formula are too high. However, while other studies have looked at differences in morbidity and iron deficiency as the primary outcome for determining if iron fortification is too high, this review expands these clinical measures in an evolutionary framework, specifically focusing on the adaptive significance of lower iron to infection risk and the infant intestinal microflora. This review proposes that the natural decline in infant iron stores—aided by the low iron content of human milk—during the first six months of life is an adaptive strategy for minimizing infection risk during weaning by limiting iron availability to pathogens. The low level of iron in human milk may reflect an evolutionarily stable strategy for humans in particular and primates in general to counterbalance the risk of infection against iron requirements for growth and development. Controlling access to iron would have had important implications for human health and may have increased human survival. This would have been especially important during complementary feeding, as the infant was introduced to nonmilk foods and the possible risks of contamination of these foods. The natural decline in iron stores also corresponds to increases in infant motor activity, a secondary risk factor for infection as infants become more mobile and interaction with the environment increases.

Current fortification practices of commercial infant formula in the United States may undermine this adaptation by providing a plentiful iron source for pathogens in addition to the excess free iron in the intestines. There is additional evidence suggesting that early excess dietary iron may be involved in the pathogenesis of multiple diseases, as well as a recent study linking excess formula iron consumption among iron replete infants with decreased childhood cognitive and visual-motor development at 10 years of age (Lozoff et al., 2006). While infants certainly require dietary sources of iron, current fortification practices may be contributing to infant health risks by overloading iron regulatory systems adapted to low levels of dietary iron and may be an additional risk to infant health from formula.

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