Homeostatic Regulation of Iron and Its Role in Normal and Abnormal Iron Status in Infancy and Childhood

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**Key Words**
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**Abstract**
Iron is important in neurodevelopment and cognitive function, and globally preventing iron deficiency and iron deficiency anemia remains a high priority. Term breast-fed infants and infants fed an iron-fortified formula usually have a satisfactory iron status during the first 6 months of life, but there are still ambiguities in assessing iron status in infants and how to properly meet their iron requirements. This is particularly evident for preterm infants, who are born with low iron stores, and for whom recommendations for iron provision vary considerably. In part, this may be due to immaturity in the regulation of iron homeostasis in young infants. Whereas 9-month-old infants appear to be able to downregulate iron absorption when being iron replete, 6-month-old infants cannot do this. Iron may be provided as drops or in iron-fortified products, but the forms provided may be metabolized differently, and excess iron in drops may cause adverse effects, possibly due to a limited ability to regulate iron absorption in young infants. Adverse effects are manifested by decreased growth: in well-nourished infants by reduced gain in length, in poorly nourished populations by lower gain in weight. The mechanism behind the decreased growth is not known, but it may involve free radical-mediated effects of iron or an interaction with zinc absorption/homeostasis. It therefore seems that iron drops should not be given to iron-replete infants.

**Introduction**
Iron serves important functions in many biochemical processes including the development of the central nervous system, and it is essential to neural myelination and neurotransmitter function [1]. The requirement for iron is particularly high during periods of rapid growth and differentiation, for example during the last trimester of pregnancy and during infancy when the brain experiences its growth spurt. Ineffective iron homeostasis during these periods may therefore result in delayed neurodevelopment and cognitive functions [2]. Many studies have shown an association between iron deficiency anemia (IDA) and poor neurodevelopment in infants [3]. Iron supplementation reduces the risk of anemia in children at risk of developing iron deficiency (ID) and IDA. On the
other hand, excessive iron supplementation of infants may lead to an increased risk of infection, poor growth and disturbed absorption or metabolism of other minerals [4]. Iron is also a well-known pro-oxidant, and non-protein-bound iron may cause formation of free oxygen radicals and increase the risk of retinopathy of prematurity in preterm infants, particularly when supplied in high doses as in blood transfusions or combined with erythropoietin (EPO) therapy [5–8]. Taken together, it is important to find optimal strategies to prevent ID at the same time as it is equally important to avoid iron overload and its potential adverse effects. Hence, it is essential to recognize which infants should be given what form of iron, in what dose, and during which period in life to achieve optimal preventive effects with minimal, if any, adverse effects. To reach this goal, a detailed understanding of how iron homeostasis in infants and children is regulated, and how the regulation varies with age, is a prerequisite.

### Development of Iron Status in Infancy

#### Term Infants

Total body iron in fetuses and newborns is approximately 75 mg/kg [9]. At a growth rate of 15–20 g/kg/day, this translates to an iron accretion rate of 1–1.5 mg/kg/day, which, however, does not apply to newborn infants since the normal decline in hemoglobin (Hb) concentration after birth causes significantly increased iron stores. Therefore, a healthy, term infant is initially independent of external iron and can double its birth weight before iron stores are depleted. At birth, blood Hb values are high, or about 170 g/l in cord blood, in healthy term infants (range 135–210 g/l), whereafter they decline with age to reach a lowest value of 110–120 g/l between 8 and 18 months of age. This decline is physiologic and is due to a breakdown of fetal Hb to be replaced by adult Hb by endogenous erythropoiesis, which is typically resumed when Hb has decreased from 170 to 120 g/l. Breast milk is low in iron (0.2–0.4 mg/l), and even though this iron is well utilized, infants breast-fed for longer than 4–6 months without receiving iron supplements or iron-fortified complementary foods are at risk of developing IDA. The magnitude of the problem may, however, have been overestimated as the cutoff for Hb for assessing anemia may not be the same as for older age groups. We have shown in a study on iron-replete infants that a more appropriate Hb cutoff at 4–6 months of age would be 105 g/l and at 9 months 100 g/l rather than the commonly used 110 g/l [10] (Table 1). Since IDA is uncommon in this age group in industrialized countries, and anemia can be due to other causes than ID, there is a need for assessing iron status of infants. Indicators of iron status include s-ferritin (s-Ft), s-protoporphyrin, s-iron, s-transferrin receptors (s-TfR), and s-transferrin saturation/total iron-binding capacity. In the healthy term infant, s-Ft is very high at birth due to large liver stores, whereafter there is a successive decrease during infancy. This decrease is physiologic and affected by growth. There is considerable tracking, but s-Ft is still affected by iron status and considered the most reliable indicator of the size of the iron stores. However, s-Ft is an acute-phase reactant and affected by infection and inflammation, and other indicators less affected by infection have therefore been suggested. The observation that 26% of healthy 12-month-old Swedish infants born at term and receiving ample quantities of iron had s-Ft levels below 12 μg/l [11], the widely accepted cutoff value for ID, raised the question whether the same cutoff values are appropriate for infants as for older children and adults. Based on the intervention study mentioned above we believe that a more appropriate cutoff at 4 months would be 20 μg/l, at 6 months 9 μg/l, and at 9 months 5 μg/l (Table 1). These calculations were based on −2 SD cutoff values in healthy, iron-replete infants born at term [10]. The ratio of log s-TfR/s-Ft, which has been suggested to be a more reliable indicator in adults, as s-TfR is unaffected by infection and indicates cellular needs for iron, does not provide any additional diagnostic value in infants [10, 12]. We found appropriate cutoffs for zinc protoporphyrin to be 75 μmol/mol heme at 4–6 months and 90 μmol/mol heme at 9 months (Table 1), and that it might be a good indicator of iron status; however, the hematofluorometer used for this assessment is rarely available in field settings [10].

#### Table 1. Suggested 2 SD cutoff values for iron status variables at 4, 6 and 9 months of age, based on iron-replete, breast-fed infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>4 months</th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/l</td>
<td>&lt;105</td>
<td>&lt;105</td>
<td>&lt;100</td>
</tr>
<tr>
<td>MCV, fl</td>
<td>&lt;75</td>
<td>&lt;71</td>
<td>&lt;71</td>
</tr>
<tr>
<td>ZPP, mol/mol heme</td>
<td>&gt;75</td>
<td>&gt;75</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Ferritin, g/l</td>
<td>&lt;20</td>
<td>&lt;9</td>
<td>&lt;5</td>
</tr>
<tr>
<td>TfR, mg/l</td>
<td>&gt;11</td>
<td>&gt;11</td>
<td>&gt;11</td>
</tr>
</tbody>
</table>

MCV = Erythrocyte mean corpuscular volume; ZPP = zinc protoporphyrin.

* Based on Swedish infants (from Domellöf et al. [10]).
**Preterm Infants**

ID is common in preterm infants [13]. Iron stores are built during the last trimester of pregnancy. Hence, compared to term infants, preterm infants have lower body iron and Hb levels at birth, as well as serum and storage iron, which is reflected by lower s-Ft and Hb concentrations, which also reach their nadirs at an earlier age than in term infants. Iron stores may be depleted already during the first months of life [14] coinciding with the onset of erythropoiesis and catch-up growth. It should be noted, however, that the relative size of iron stores at birth in preterm infants is not known. Furthermore, while a term infant doubles its birth weight in about 5 months, a preterm infant will do so in 1–2 months. In very low-birth-weight (LBW) infants, iron losses due to phlebotomy can amount to 6 mg/kg/week [15]. To some extent, this is balanced by the fact that a red blood cell transfusion typically adds about 8 mg/kg of iron. Obviously, routines for blood sampling, blood transfusion and EPO treatment influence iron requirements of preterm infants. Of note is also that iron absorption from iron supplements given between feedings is 25–40% in preterm infants, which is higher than in term infants [16]. Iron absorption from preterm formula was reported to be 11% [17]. Studies are lacking on iron absorption from multinutrient-fortified human milk or from iron supplements given with human milk. Yet, absorption from these sources can be assumed to exceed that from preterm formula, as in term infants iron absorption from human milk is significantly higher than that from formula [18]. Taken together, in contrast to term infants, in whom ID typically develops after the first half of infancy, preterm infants are at risk of ID already during the first half of infancy. Preterm infants of low gestational age or of lower birth weight are at particular risk of developing ID as are preterm infants in low-income countries and those exclusively breast-fed without iron supplementation [13, 19]. Iron supplementation and/or blood transfusion are therefore routinely used to prevent IDA. However, the proper level and timing of iron supplementation is still controversial, although the ESPGHAN Committee on Nutrition [16] recently recommended an intake of 2–3 mg/kg/day, corresponding to 1.8–2.7 mg/100 kcal, and that prophylactic enteral iron supplementation (given as a separate iron supplement, in preterm formula or in fortified human milk) should be started at 2–6 weeks of age (2–4 weeks in extremely LBW infants). Infants who receive EPO treatment and infants who have had significant, uncompensated blood losses may initially need a higher dose, requiring a separate iron supplement in addition to preterm formula or fortified human milk. However, enteral iron doses >5 mg/kg/day should be avoided in preterm infants due to the risk of retinopathy of prematurity. Iron supplementation should be delayed in infants who have received multiple blood transfusions and have high s-Ft concentrations [20]. Iron supplementation should be continued after discharge, at least until 6–12 months of age, depending on the diet.

With the premises that it is likely that LBW infants weighing more than 2,000 g at birth are less likely to develop early ID than those weighing less than 2,000 g, and that the proper dose and time of supplementation had not been properly studied, Berglund et al. [21] in a recent double-blind, randomized, placebo-controlled intervention trial encompassing close to 300 nonanemic and otherwise healthy marginally LBW infants, i.e. infants weighing 2,000–2,500 g at birth, representing 3–5% of all newborn infants in affluent countries, including both late preterm infants and LBW term infants, studied the effect of supplementation with iron drops (iron succinate) at 1 or 2 mg/kg body weight per day divided into 2 daily doses from 6 weeks to 6 months of age. They concluded that this group is at greater risk than term infants of developing early IDA, and that LBW and breast-feeding seem to have a synergistic negative effect on iron status at 6 months. In contrast, we and others have previously shown that the prevalence of ID in exclusively breast-fed term infants of normal birth weight (>2,500 g) is less than 1% in similar populations [19, 22]. Berglund et al. [21] found a lower, but not significantly lower, prevalence of ID in the group receiving 2 mg iron/kg/day compared to 1 mg/kg/day and calculated that a relatively low iron intake is sufficient to prevent ID and IDA. An intake of 0.25 mg/kg/day effectively prevented these marginally LBW infants from IDA at 6 months, while an intake of 1.0 mg/kg/day prevented ID, which should be covered by formulas containing 8 mg iron/l. No adverse effects on growth or morbidity were observed with either of the iron doses, not even on growth of iron-replete infants. Berglund et al. [21] further observed that in the placebo group there was a trend towards better iron status in term compared to preterm marginally LBW infants, and although the difference was not significant, the prevalence of ID and IDA was higher in preterm infants. As the difference was not explained by differences in iron intake, they concluded that there might be differences in iron metabolism or in iron stores at birth between term and preterm marginally LBW infants.
**Factors Affecting Iron Status in Infancy**

**Iron Endowment at Birth**

Maternal ID does not appear to compromise the iron endowment of their infants, but severe ID, i.e. IDA, does have an adverse effect on iron status of the newborn. Infants of moderately and severely anemic mothers have lower iron stores and a 3-fold increased risk of LBW, placing them at higher risk of ID at an early age. Indeed, the incidence of ID and IDA during late infancy is higher in infants born to mothers with IDA than in infants born to iron-replete mothers [20, 23–28]. The timing of umbilical cord clamping also affects the iron endowment of the newborn. Early cord clamping decreases iron transfer to the infant, whereas delayed cord clamping increases the red cell volume in the infants and, in turn, increases the iron endowment. A 2-min delay in umbilical cord clamping increases total body iron by about 33%, resulting in greater iron stores at 6 months of age [29–31]. Taken together, iron requirements during the first half of infancy depend greatly on the iron endowment of the infant at birth.

**Effect of Gender on Iron Status**

Even if there is no difference in the estimated iron requirements between boys and girls during infancy, substantial sex differences in iron status have been observed at that age [32, 33]. Hb, mean corpuscular volume and s-Ft concentrations were found to be lower and TfR and zinc protoporphyrin concentrations to be higher in boys than in girls at 4, 6 and 9 months of age. Moreover, boys at 9 months of age had a higher risk of being classified as having IDA than girls [32]. The sex differences in mean corpuscular volume and zinc protoporphyrin concentrations may reflect normal physiologic differences between genders. On the other hand, the differences in Hb and TfR seem to reflect a higher incidence of ID in boys. Sex-specific reference values to define ID may need to be developed for some of the iron status indicators [32].

**Provision of Various Forms of Iron**

In many countries, it is recommended to give iron supplements as iron drops to breast-fed infants after the first 4–6 months of age. We compared the effects of initiating iron supplementation at 4 months as compared to 6 months until 9 months of age in exclusively breast-fed infants in 2 different settings: Honduras as an example of a developing country with low iron endowment at birth and frequent IDA at an early age and Sweden as an example of a population with adequate iron stores at birth and low prevalence of IDA in infancy [19]. We found no significant benefits of starting iron supplementation at 4 months as compared to 6 months of age in either setting. It was evident, however, that the Honduran infants benefited from the supplement after 6 months of age as shown by Hb values, several indicators of iron status and the prevalence of ID at 9 months. In contrast, no effects of the supplements were found in the Swedish infants at any age. This suggests that exclusive breast-feeding until 6 months of age when combined with complementary food of high quality and rich in iron will meet the iron requirement of infants. Unexpectedly, we found that iron supplements given to iron-replete infants resulted in decreased linear growth in both settings (see below).

The form of iron given to infants may affect indicators of iron status differently. We have shown that infants provided iron-fortified cereals between 6 and 9 months of age had significantly higher Hb concentrations than infants given the same amount of iron daily in the form of iron drops (fig. 1) [34]. In contrast, the infants given iron drops had significantly higher s-Ft concentrations than those fed iron-fortified cereals. This suggests that these 2 forms of iron are metabolized differently, with iron from drops preferentially being deposited in stores, whereas iron in fortified foods is incorporated into erythrocytes. Further studies are needed to elucidate the mechanisms behind these observations.

It is a generally held opinion that iron from human milk is much better utilized than from infant formulas. This is likely due to considerable differences in nutrient composition of breast milk and infant formula. Therefore, the iron content in formulas has typically been substantially higher, i.e. 25–60 times higher than in human milk. Recent studies, however, have shown smaller differences in iron absorption between human milk and infant formulas. Consistent with these observations, we have shown that a considerably lower level of iron fortification of infant formulas results in adequate iron status, which is not different from breast-fed infants until 6 months of age [35, 36]. Healthy Swedish infants fed a formula providing 1.6 mg of iron/l from 1 month of age were shown to have satisfactory iron status at 6 months of age [36]. Infants born with low iron status may need more iron, but it is uncertain whether higher levels of iron fortification of infant formula will result in improved iron status of formula-fed infants up to 6 months of age as iron supplementation of Honduran infants (with low iron endowments) before 6 months of age failed to improve iron status [19]. Most infant formulas marketed presently contain 4–12 mg of iron/l, which is at least 10–30 times high-
er than the level of iron in breast milk. It may be questioned whether infant formula used during the first 6 months of life should contain a vast excess of iron which provides no benefit in order to cover perceived increased iron requirements during 6–12 months of age. In areas where the same type of infant formula is used during the first 12 months of age, increasing the level of iron fortification in complementary foods may be an alternative possibility, while in areas where different types of milk formulas are used between 0–6 and 6–12 months of age, the follow-on formula may have a higher level of iron fortification [37].

Although the magnitude of the difference in bioavailability of iron between breast milk and infant formula varies among studies, most investigators agree that iron is better absorbed from breast milk. In part, this may be due to the iron-binding protein lactoferrin, which is present in high concentrations in breast milk, but virtually absent in infant formula [38]. A major part of iron in breast milk is associated with lactoferrin. Lactoferrin is relatively resistant against proteolysis and has been found intact in the stool of breast-fed infants [39]. Human lactoferrin has been shown to be taken up by the intestinal cell via a specific lactoferrin receptor (fig. 2), and studies on human intestinal cells have shown that the protein as well as bound iron are internalized [40]. Thus, this provides a unique mechanism for utilization of breast milk iron. In contrast, iron in infant formula based on cow’s milk is largely bound to casein, and phosphopeptides formed during digestion may limit iron absorption [41].

Breast milk contains less casein than cow’s milk and different casein subunits, and relatively more iron is instead found in low molecular complexes, a form of iron which is likely to be comparatively well utilized. Infant formulas contain higher levels of calcium than breast milk does, particularly formulas for preterm infants, which has caused some concern as calcium has been shown to lower iron absorption in adults [42]. This inhibitory effect may, however, only occur in short-term isotope studies as long-term studies on infants given high levels of calcium fail to show any adverse effect on iron status.

**Iron Absorption in Infants and Its Regulation**

As mentioned above, recent studies on iron absorption in infancy using stable isotopes have revealed less pronounced differences in iron absorption from breast milk

![Fig. 1. Hb (a) and s-Ft (b) concentrations at 6 and 9 months of age. Mean (95% confidence interval) Hb at 6 months (baseline) and 9 months, and mean (95% confidence interval) s-Ft at 6 months (baseline) and 9 months in infants receiving iron-fortified foods (FF, daily intake >1.3 mg/kg/day and no iron drops), infants receiving medicinal iron drops (MD, 1 mg/kg/day in addition to the habitual diet) and in infants with low iron intake (LI, daily intake <1.3 mg/kg body weight and no iron drops). The cutoff of 1.3 mg/kg/day was chosen to achieve similar total iron intake in the MD and FF groups. Bars not sharing a common letter are significantly different at p ≤ 0.002 (ANCOVA). Age × group interaction is significant at p < 0.05 (reproduced from Domellöf et al. [34] with permission).](image-url)
and infant formula. In the past, radioisotope methodology was used, and usually substantial differences in iron bioavailability were found between breast milk and cow’s milk formula [43]. This method has the advantage that absorbed and retained iron is actually measured by whole-body counting. However, iron absorption is also strongly affected by iron status, and this was rarely controlled for in these studies. Stable isotopes have commonly been used during recent times, and such studies show smaller or no differences between breast milk and infant formula. This may be due to improvements in infant formula composition, but possibly also due to methodological limitations. In stable isotope studies, it is assumed that absorbed iron is incorporated into red blood cells at about 80% [44], a value that has been derived from studies on human adults. In fact, much less iron is incorporated into erythrocytes in infants [45], which may cause an underestimate of actual iron absorbed. The extent to which this incorporation is affected by age or by iron status is not yet known, nor how it is affected by the form of iron given to the infant. As described above, iron given as drops or as fortification was shown to affect iron indicators differently, suggesting different metabolic pathways. Whether iron taken up from breast milk (lactoferrin) or from infant formula has a different metabolic fate is not yet known.

Using stable isotope methodology, we have shown that 6-month-old healthy, exclusively breast-fed infants born at term absorbed 16.4 ± 11.4% of iron, with no significant difference between iron-supplemented and unsupplemented infants [46]. At 9 months of age, iron absorption from human milk remained at the same level in iron-
supplemented infants (16.9 ± 9.3%). Whether there are age-related differences in iron absorption independent of iron status is not known as there have been no developmental studies on iron absorption in iron-replete infants by the same investigators using the same technique. A compilation of studies to date indicates that this is not the case although the results are highly variable, but differences in iron status and methodology between studies may obscure such a finding. Homeostatic regulation of iron absorption in infants also needs to be considered. Although no difference was found between iron-supplemented and unsupplemented infants at 6 months of age, unsupplemented infants had considerably higher iron absorption at 9 months of age, i.e. 36.7 ± 18.9% (p = 0.01) [46]. This strongly suggests that homeostatic regulation of iron absorption is absent in young infants but matures and is present at 9 months of age. In further support of this, iron supplementation between 4 and 6 months of age considerably increased Hb concentration regardless of initial iron status. In contrast, continued iron supplementation up to 9 months had no effect on Hb concentrations in iron-replete infants [19]. It is not yet known when iron homeostasis develops during the period of 6–9 months, nor whether it is fully developed at 9 months of age. Further studies of various age groups are needed to clarify this.

Molecular Regulation of Iron Absorption

The primary importer of iron across the apical membrane of the intestinal epithelial cell is divalent metal transporter 1 (DMT1) (fig. 1). This transporter is responsible for the uptake of ferrous iron and is strongly regulated by iron status [47]. While duodenal cytochrome b (dcytb), a ferric reductase located at the apical membrane, has been shown to be involved in the regulation of iron metabolism in rodents [48], there are limited data supporting this occurring in humans. In fact, this would be unlikely as humans are known to poorly absorb ferric iron, and recent observations in human subjects with highly varying iron status (hereditary hemochromatosis, ID, controls) indicated no differences in dcytb expression depending on iron status [49].

Following uptake of ferrous iron by the enterocyte, iron is translocated across the cell and exported by ferroportin (FPN) located at the basolateral membrane (fig. 1). FPN is also strongly regulated by iron status. Following the export of iron by FPN, iron will be transported to the liver, bound to transferrin and utilized by the reticuloendothelial system for Hb synthesis, or deposited as iron stores. The communication between the iron stores in the liver and the intestinal epithelial cell was long an enigma but recently found to be mediated by hepcidin, a peptide synthesized by the liver [50]. Hepcidin acts as an endocrine regulator of iron metabolism by covalently binding to FPN and causing its internalization and breakdown. Iron subsequently accumulates in the intestinal cell and then downregulates the expression of DMT1. As a consequence of these events, iron absorption is effectively downregulated. The molecular reasons for the lack of homeostasis of iron metabolism that we found in young infants are not yet known, but results from rodent models may provide some insights. It has been found that 10-day-old suckling rat pups also lack homeostatic regulation of iron absorption, whereas 20-day-old weaned pups can regulate iron absorption [51]. At day 10, there was no effect of iron status on either DMT1 or FPN expression in intestinal epithelial cells. However, at day 20, ID strongly upregulated the expression of these 2 iron transporters, and iron supplementation strongly downregulated their expression. Whether the same kind of regulation occurs in human infants is not yet known. It is tempting, though, to speculate that the offspring is adapted to absorb as much iron as possible as long as milk with its low iron content is the main food.

Anemic premature infants are usually treated with EPO in combination with iron supplements and/or blood transfusions. It is likely that these treatments may affect hepcidin expression in different ways [2]. Treatment with EPO enhances erythropoiesis which will cause downregulation of hepcidin expression, thereby increasing iron absorption and mobilization from stores. Injection of EPO into adult rats resulted in a redistribution of iron due to enhanced erythropoiesis [52]. Iron was released from the liver, serum iron decreased and intestinal iron absorption increased. This was accompanied by increased expression of DMT1 and dcytb that reduces ferric iron to the ferrous form. It is likely that this was a consequence of downregulation of hepcidin expression as suppression of erythropoiesis increases hepcidin expression, and anemia caused by phlebotomy results in decreased hepcidin expression, but only if erythropoiesis was on-going as a response to the anemia. Blood transfusions would increase the number of erythrocytes and plasma iron concentration, which in turn increase hepcidin expression. Therefore, regulating iron supply and optimizing erythropoiesis in preterm infants is a difficult task.
Adverse Effects of Iron Supply

Iron is unique inasmuch as in contrast to the regulation of absorption there is no natural route for excreting excess iron. Thus the possibility of overload certainly exists and is well known in adults. However, iron overload as such has not been recognized in term human infants, and is only implicated in premature infants with a known, or feared, consequence of increased iron-associated oxidative damage. Indications of excessive iron intakes by infants have recently been observed in some studies. As mentioned above, we noticed that supplementation of Swedish healthy, term breast-fed infants with iron drops caused decreased linear growth by 9 months of age [53]. Since this adverse effect was not noted in Honduran infants, we hypothesized that the adverse effect was due to the iron-replete status of the Swedish infants. Indeed, when the Honduran cohort was divided into iron-replete and non-iron-replete infants, an adverse effect on growth was observed in the iron-replete group. A few other studies have also shown negative effects of iron supplements on growth [27, 54, 55]. However, in those studies the effect was noted for weight gain rather than linear growth. It should be noted, though, that the nutritional status of the infants in those studies was compromised overall, which is known to decrease linear growth and cause stunting. Thus, when linear growth is compromised, it is possible that the adverse effect of excess iron may be manifested differently and instead affects weight gain. However, a recent study on breast-fed US infants given iron drops showed both a significant reduction in length gain and a trend towards reduced weight gain as compared to infants given iron-fortified cereals [56]. The mechanism(s) behind the adverse effect of excess iron is/are still not known, but may involve pro-oxidative effects of excess iron or, possibly, an interaction between iron and nutrients involved in growth, such as zinc [57].

References


