Benefits and Harms of Iron Supplementation in Iron-Deficient and Iron-Sufficient Children

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Abstract

Due to high iron requirements, young children are at risk for iron deficiency anemia. Iron supplements are therefore often recommended, especially since iron deficiency anemia in children is associated with poor neurodevelopment. However, in contrast to most other nutrients, excess iron cannot be excreted by the human body and it has recently been suggested that excessive iron supplementation of young children may have adverse effects on growth, risk of infections, and even on cognitive development.

Recent studies support that iron supplements are beneficial in iron-deficient children but there is a risk of adverse effects in those who are iron replete. In populations with a low prevalence of iron deficiency, general supplementation should therefore be avoided. Iron-fortified foods can still be generally recommended since they seem to be safer than medicinal iron supplements, but the level of iron fortification should be limited. General iron supplementation is recommended in areas with a high prevalence of iron deficiency, with the exception of malarious areas where a cautious supplementation approach needs to be adopted, based either on screening or a combination of iron supplements and infection control measures.

More studies are urgently needed to better determine the risks and benefits of iron supplementation and iron-fortified foods given to iron-deficient and iron-sufficient children.

Introduction

Iron deficiency anemia (IDA) is the most common micronutrient deficiency worldwide with an estimated 600 million affected individuals [1]. Young children are a special risk group due to rapid growth leading to high iron
requirements. Iron is essential for the development of the central nervous system and there is an established association between IDA in young children and poor neurodevelopment. It is therefore important to prevent iron deficiency in young children, and iron supplements are often recommended to this risk group. The period of highest iron requirement occurs at 6–12 months of age when dietary requirements are estimated to be about 1 mg/kg per day [2]. Even in affluent societies, this intake is difficult to achieve without iron-fortified foods or separate iron supplements.

However, in contrast to most other nutrients, excess iron cannot be excreted by the human body, and it has recently been suggested that excessive iron supplementation of infants may have adverse effects on growth [3], risk of infections [4], and even on cognitive development [5]. Thus, recommendations regarding iron intake must not only prevent iron deficiency but must also avoid unnecessary iron supplementation of iron-sufficient infants.

**Anemia**

Many studies in children have shown that iron supplements as well as iron-fortified foods effectively increase the blood hemoglobin concentration (Hb) [2]. Indeed, the Hb response to iron treatment has long been known as a gold standard to diagnose IDA [6]. Theoretically, iron supplements should increase Hb only in those children who are initially iron deficient. It is more difficult to assess the effects of iron supplements in iron-sufficient children since almost all studies are carried out in risk groups, e.g. populations with a high prevalence of iron deficiency. In a randomized, controlled iron supplementation trial in Swedish and Honduran breastfed infants, we showed that iron supplements given before 6 months of age increased Hb even in those infants who

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**Fig. 1.** The balance between adverse effects of iron deficiency and adverse effects of iron overload.
were initially iron replete and that Hb response to iron supplementation was useful for the diagnosis of IDA only after 6 months of age [7].

**Brain Development**

Growth and development of the central nervous system is rapid during the first years of life. Iron is critical for brain development since it is essential for myelination, monoamine synthesis and energy metabolism in neurons and glial cells [8]. In animal models of iron deficiency, reduced motor activity has been the most consistent observation [9]. Negative effects on cognitive and behavioral functions have also been observed in some studies of iron-deficient animals [8]. In most of these animal studies, neurological function has not been fully restored after iron repletion [9].

Several well-performed case control studies in children have shown a consistent association between IDA and poor cognitive and behavioral performance even though these observations may be confounded by other nutritional deficiencies and socioeconomic factors [9, 10]. Most clinical trials of iron supplementation in children unfortunately have not included neurodevelopmental outcomes. A meta-analysis of seventeen randomized clinical trials in children that included cognitive outcomes showed that iron supplementation had a significant but modest positive effect on mental development index of 1.5–2 points of 100 [11]. This effect was more apparent for children who were initially anemic, suggesting that iron supplements have positive cognitive effects in iron-deficient children. This meta-analysis showed no convincing evidence for an effect of iron supplements on neurodevelopmental outcomes in children below 2 years of age. This lack of effect in the youngest infants may be due to irreversible effects of iron deficiency on the developing brain or the fact that cognition and behavior is more difficult to test in young children. The possibility that iron deficiency leads to irreversible effects in young children is a strong argument for prevention. There are very few trials of preventive iron supplementation in young children in which neurodevelopmental outcomes have been assessed. In one trial in Indonesia, a positive effect of 10 mg iron daily given from 6 to 12 months of age was observed on Psychomotor Development Index at 12 months (106 vs. 103 in the placebo group) [12]. This may not have been a purely preventive trial since 41% of the infants had anemia at baseline.

There are a few recent studies suggesting that excessive iron intake can have negative effects on brain development. In a mouse model, Parkinson-like progressive midbrain neurodegeneration was seen after a period of high dietary iron intake [13]. These findings are supported by preliminary data from a randomized controlled trial (RCT) in which healthy Chilean infants with a birthweight of $\geq$3 kg and without IDA at 6 months of age were randomized to receive fortified formula with a high (12 mg/1) or low (2.3 mg/1) iron
content from 6 to 12 months of age [5]. Motor development, cognitive development, spatial memory, reading and arithmetic and visual-motor integration were assessed at 10 years of age. The high iron group had lower scores on all of these outcomes, significantly so for spatial memory and visual-motor integration scores. Effects depended on initial iron status: High iron formula had a more negative effect on the outcome measures in children who were initially iron sufficient (higher Hb), while the opposite was true in infants with an initial lower Hb. The effect size in visual-motor integration was 2 standard deviations corresponding to a score difference of 15 points out of 100. The physiological mechanisms behind this possible negative effect of excessive iron intake on cognitive development are unknown but iron-mediated oxidative stress has been suggested [13].

**Growth**

Most iron supplementation studies in children show no overall effect of iron on growth, although a few studies in iron-deficient infants have shown a positive effect, and some recent studies have suggested that iron supplements given to iron-sufficient children may have a negative effect on growth [14].

In a recent meta-analysis of the effects of micronutrients on growth of children under 5 years of age, twenty-seven randomized, controlled studies of iron supplementation were included [15]. In this meta-analysis, there was no significant overall effect of iron supplements on either weight or length gain. There were also no significant differences when studies were stratified by mean baseline Hb. However, without access to original data it was not possible to investigate the possible interaction between baseline Hb (or iron status) and iron supplements on growth at the individual level.

Four studies to date have shown a negative effect of iron supplements on the growth of young children. In contrast to other studies, these have stratified the children individually based on initial iron status. Idjradinata et al. [16] investigated the effect of iron (3 mg/kg daily) during 4 months in iron-sufficient 12- to 18-month-old children in Indonesia and observed a significantly lower weight gain in the iron group (560 vs. 848 g; p = 0.02). The growth of the iron-deficient, anemic children in the same study was improved by iron supplementation. In a study of breastfed Swedish and Honduran infants, we showed that iron supplementation (1 mg/kg daily) from 4 to 9 months of age had a negative effect on length gain [3]. This effect was restricted to the more well-nourished Swedish infants and to Honduran infants with an initial Hb of >110 g/1. In infants with initial Hb <110 g/1, no effect on length gain was observed. Majumdar et al. [17] randomized 100 iron-replete children (6–24 months old) to receive iron supplements (2 mg/kg daily) or placebo, while 50 iron-deficient children received 6 mg/kg daily during 4 months. Compared to the placebo group, iron supplementation resulted in a significantly increased
weight and length gain in iron-deficient children, but a significantly decreased weight and length gain in iron-sufficient children. Most recently, Lind et al. [18] investigated the growth of iron-replete Indonesian infants from an iron supplementation trial. In this study, 680 infants were randomized to receive iron supplements (10 mg daily) with or without zinc supplement from 6 to 12 months of age. No overall effect of iron on growth was observed, but when infants were stratified by initial iron status, a significant negative effect of iron supplementation on weight gain was observed in those infants who were initially iron replete (n = 154). The effect was substantial with a difference of >400 g between iron supplemented and non-supplemented iron-replete infants. Iron-supplemented, iron-replete infants also had significantly lower serum zinc concentrations.

The mechanism behind the possible negative effect of iron supplementation on growth in iron-sufficient young children is not known. An interaction with zinc absorption or zinc metabolism has been suggested (see also below) since it is known that zinc deficiency has a negative effect on growth [19]. The finding of lower serum zinc concentrations in iron-supplemented iron-replete infants in the study by Lind et al. [18] would support that hypothesis. However, in our previous study, no difference in serum zinc was observed [3]. Other possible mechanisms include pro-oxidative effects of iron or a decreased dietary intake due to gastrointestinal side effects of iron supplements or an increased susceptibility for gastroenteritis. In our study, iron supplements increased episodes of diarrhea in iron-sufficient infants, while the opposite was observed in iron-deficient infants [3].

Infections

In addition to the immune response, host organisms can combat pathogens by depleting them of essential nutrients. Iron has a pivotal role in the defense against infections since it is essential for the growth of virtually all pathogens – bacteria, protozoa and viruses. As a part of the acute phase response in humans, free iron is depleted from the systemic circulation down to $10^{-24}$ M. The mechanism is believed to involve the induction of hepcidin production in the liver, leading to a downregulation of intestinal iron absorption and sequestration of iron in reticuloendothelial macrophages [21]. Ferritin – an iron-sequestering protein – is also increased as part of the acute phase response, further contributing to the reduction of iron available for pathogens. Conversely, microorganisms – especially bacteria – have evolved elaborate methods for iron retrieval to be able to cause invasive infections in humans [22].

This delicate balance between host and pathogen may be disturbed by iron supplementation and it has indeed been suggested already in the 1800s that iron supplements could increase the risk of infection. Two meta-analyses on
the subject in 2001–2002 came to conflicting conclusions. Gera and Sachdev [23] found no overall increase in infections except for an increased risk of diarrhea. Oppenheimer [24], however, found that iron supplementation was associated with an increased risk for clinical attacks of malaria and other infections in malarious regions. The increased risk for infections was particularly observed in trials in which parenteral or high-dose oral supplementation (>2 mg/kg per day) was used.

Interestingly, the malaria parasite is unable to utilize heme iron even though it grows in red blood cells, surrounded by an abundance of Hb [25]. Instead, plasmodia are dependent on the very small pool of free iron in the cytoplasm, making them susceptible to changes in iron concentrations caused by nutritional factors.

In 2003, a large RCT of iron supplementation in Pemba, Zanzibar, had to be terminated due to serious adverse effects [4]. In this trial, 24,076 children aged 1–35 months were randomized to daily oral supplementation with iron (12.5 mg) and folic acid (with or without zinc) or placebo. The dose of iron was halved in infants <12 months. In the groups receiving iron and folic acid, there was a 15% increased risk of death and an 11% increased risk of hospital admission. A substudy suggested that the risk for serious adverse events was higher in infants who were initially iron replete, i.e. those with higher Hb and lower zinc protoporphyrin. These results were later supported by an RCT in Peruvian children (0.5–15 years), showing that iron supplementation (15 mg daily) resulted in an increased morbidity due to Plasmodium vivax malaria [26].

Using the same study design as the Zanzibar trial, another large RCT was performed in a region with a low prevalence of malaria (southern Nepal) [27]. In this trial, iron supplementation resulted in a significant reduction in anemia but no increased risk for death, diarrhea, dysentery or respiratory infections.

Taken together, these studies suggest that iron supplementation of children is safe with regard to severe infections in nonmalarious regions. In malarious regions, iron-deficient children are likely to benefit from iron supplementation, while there is an increased risk for severe malaria infections in those who are iron sufficient.

Interactions with Other Minerals

Since there is no mechanism for iron excretion in humans, regulation of iron absorption is critical. The molecular mechanisms for iron absorption in the intestine have recently been characterized, and the main iron transporter is believed to be divalent metal transporter 1 (DMT1) at the apical membrane and ferroportin 1 at the basolateral membrane of the enterocyte [2]. There are possible metabolic interactions between iron and several other minerals.
Lead

Lead exposure in children may lead to poor cognitive performance, especially in children with blood lead concentrations >10 µg/dl but also at lower levels. Iron deficiency in children is a risk factor for lead poisoning, and it has been suggested that this is caused by an upregulation of DMT1 in a state of iron deficiency, leading to an increased intestinal absorption of lead. Thus, iron supplementation of iron-deficient, lead-exposed children may reduce the adverse effects of lead exposure. Some studies indeed indicate that iron supplements given to iron deficient, lead-exposed school children, reduce blood lead concentrations, but there is yet no evidence that this results in improved cognitive performance [2].

Zinc

Zinc deficiency often coexists with iron deficiency in young children in developing countries, and combined iron and zinc supplementation is therefore often recommended. However, a competitive inhibition of iron on zinc absorption has been suggested, possibly resulting in a negative effect of iron supplementation on zinc status.

Possible interactions between iron and zinc in clinical supplementation trials have been reviewed in 2005 [28]. In nine of ten reviewed trials of iron-only supplementation given to children, there was no effect of iron supplementation on serum zinc. In all four reviewed trials of combined iron and zinc supplementation, the addition of iron to zinc supplements had no adverse effect on serum zinc. However, it is important to realize that, even though there is no better biomarker, serum zinc is not a sensitive marker of zinc status, especially not in mild and moderate zinc deficiency.

Regarding functional outcomes, a few trials have suggested a negative effect of the addition of iron to zinc supplements. Berger et al. [29] showed in 2006 that the addition of iron reduced the positive effect of zinc on serum zinc and weight gain. Similarly, as mentioned above, Lind et al. [18] showed that combined supplementation had less positive effect on growth than zinc supplementation alone and that iron supplementation of iron-replete infants resulted in poorer weight gain and lower serum zinc concentrations.

Even though iron and zinc are chemically similar, they do not seem to share the same absorptive pathway in the intestine since zinc is mainly shuttled across the enterocyte by specialized zinc transporters (Zip-4 and ZnT-1) [30]. We have recently shown in a stable isotope study that iron supplements do not reduce intestinal zinc absorption in healthy, breastfed infants [31]. This, however, does not exclude other mechanisms of interaction.

Copper

There are several known interactions between iron and copper metabolism, and these two minerals have a common apical enterocyte transporter (DMT1) [2]. We have shown that iron supplementation of infants reduced
copper-/zinc-dependent superoxide dismutase activity, suggesting a negative effect on copper status [32]. However, this effect may be due to interactions beyond the absorption step, since we and others have shown that iron supplements do not reduce copper absorption in infants [31, 33].

**Mode of Administration**

In almost all studies that have demonstrated adverse effects of iron in iron-replete children, medicinal iron supplements (iron drops) have been used rather than iron-fortified foods. This prompted us to investigate the possibility that medicinal iron supplements have different physiological effects than iron-fortified foods. In a secondary analysis of two clinical trials, we compared infants who had received the same dose of iron from medicinal iron drops and from iron-fortified foods [34]. Interestingly, iron given as medicinal iron drops increased serum ferritin, suggesting that it was primarily deposited into iron stores, while iron given as iron-fortified foods increased Hb, suggesting that it was primarily used for Hb synthesis. We speculate that a dose of iron given once daily gives a higher peak of serum iron, inducing hepcidin which diverts iron to storage. It is possible that such peaks of serum iron, possibly leading to higher concentrations of free iron, would increase the risk for adverse effects, especially in iron-replete infants.

**Conclusions**

In conclusion, there are now several studies suggesting that even though iron supplements given to iron-deficient children may reduce anemia, improve cognitive outcome and even improve growth and reduce the risk of infections, iron supplements given to iron-replete children may instead have adverse effects on infections (malaria), growth and possibly even cognitive development. With one exception, these adverse effects were only observed in infants receiving medicinal iron supplements.

The most severe adverse effect is the increased malaria-related mortality. The implication in malarious regions is that general iron supplementation of children should be avoided. In those regions, a cautious supplementation approach needs to be adopted, based either on screening or the combination of iron supplements or iron-fortified foods with infection control measures.

The implication with regard to growth is more complicated. Since the growth inhibition is not likely to be permanent and since iron supplements have important positive effects in iron deficient children, general iron supplementation should not be discouraged in areas with a high prevalence of iron deficiency. However, in populations with a low prevalence of iron deficiency,
general supplementation should be avoided. Iron-fortified foods at current levels are probably safe in this respect.

The most difficult problem is how to assess the risk for poor cognitive development in young children receiving high doses of iron-fortified foods. This concern is based on a single study in humans and needs to be verified. Nevertheless, manufacturers of iron-fortified foods for infants and young children should probably avoid very high doses of iron fortification.

More studies are urgently needed to better determine the risks and benefits of iron supplementation and iron-fortified foods given to iron-deficient and iron-sufficient children. It is important that all clinical trials of iron supplements and iron-fortified foods in children include functional outcomes and long-term follow-up.

**References**

Domellöf


Discussion

Dr. Daniel: I noticed that in your cohorts the premature babies tended to be the larger preterms in the late 30 weeks of gestation. We have talked a great deal about the very low birthweight preterm infants and the poor growth and neurological outcomes in this group of babies. Would you care to comment on the effect of anemia of prematurity and relative iron deficiency at that point in time on poor growth and poor neurological outcome?

Dr. Domellöf: The smallest preterms are at the highest risk for iron deficiency and therefore need iron supplements to prevent iron deficiency anemia with the ultimate
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goal to improve neurological outcome. However, in those infants who have received multiple blood transfusions, you should check serum ferritin before you start iron supplementation to ensure that they do not have iron overload [1]. Also, you should not expect iron supplements to be effective against early anemia in preterms, which is generally mostly due to anemia of prematurity [2]. The iron deficiency anemia comes later, usually only after the baby has doubled his/her birthweight.

Dr. Endyarni: I know that we have different stages in iron deficiency: iron depletion, iron deficiency and iron deficiency anemia. If we wait until the child has reached the stage of iron deficiency anemia, I think it’s too late for us to give supplementation. At which stage according to you should iron supplementation be given, and which one do you prefer? We give a low dose over a longer period, but in iron deficiency anemia, for instance, should we not apply a short-course high-dose regimen and then do the follow-up? Which one is better according to you?

Dr. Domellöf: In a high-risk group, it’s better to prevent the development of iron deficiency anemia with a low dose of iron supplements, but in a patient who has already developed iron deficiency anemia, you should start with a high dose for a short time to reverse the anemia and then you might either improve the diet or you could continue with a lower dose of iron supplement to prevent relapse of the anemia.

Dr. Endyarni: Almost 60% of our young girls have anemia. According to your experience, when should we perform the screening for anemia again?

Dr. Domellöf: Adolescent girls normally have a lower hemoglobin and ferritin compared to boys, so first of all you should make sure that you use a relevant definition of anemia and iron deficiency anemia [3]. Second, you should make sure that the anemia indeed is iron deficiency anemia since there are also many other causes of anemia [4]. If you indeed have a large proportion of iron deficiency anemia, you should aim to prevent this, and there are many studies showing that iron supplementation programs in schools can be effective [5].

Dr. Gillman: I wanted to ask you to speculate a little bit more about fortification and about the benefits, risks and costs in iron-replete vs. iron-deficient societies. Given all of the harms that you showed for iron-replete people, what is the justification for iron fortification in iron-replete societies today? And then one of your slides showed that iron fortification costs more than iron supplementation, and I wonder if that’s really true in the long run in iron-deficient societies and whether iron fortification in iron-deficient societies is a cost-effective measure.

Dr. Domellöf: Iron supplements have a long shelf life so they are usually easier and cheaper to use in preventive programs in a low income setting. However, to achieve a sustained effect in a society, it is probably better to improve the availability of affordable iron-rich foods and iron-fortified foods. I think this is an important reason why we have much less anemia in European infants compared to infants in developing countries. However, the optimal level of iron fortification in infant foods is not known and I think we need more research on that.

Dr. Haschke: I have a comment on your recommendations how to deal with populations where malaria is prevalent. Do you really think that we can make any recommendations before we understand the mechanisms how iron interacts with the host in these regions?

Dr. Domellöf: Unfortunately, the Pemba trial will lead to reluctance to perform more trials even though this is necessary in order to be able to make good recommendations. Infection control measures can reduce malaria-related child mortality very significantly, so I think that a trial of iron supplementation combined with malaria infection control could be one way to go [6].

Dr. Haschke: The costs of such a trial may be a limiting factor.

Dr. Domellöf: Yes, the cost is a problem but it might still be possible [6].
Dr. Ziegler: I don't know where the dose of 1 mg/kg per day or 7 mg/day comes from. Do you think that a lesser dose, such as 0.5 mg/kg per day might be effective in preventing iron deficiency in most infants and at the same time have no effect on growth in iron-sufficient infants?

Dr. Domellöf: The recommended dose was calculated a long time ago and it's based on a lot of assumptions [7], so I think we don't know enough about the real requirements. We also have to consider that an iron-deficient child will upregulate intestinal iron absorption and thereby retain enough iron even when dietary iron intake is low. Actually, unpublished data from our current trial in marginally low birthweight infants suggest that a quite low dose of iron is sufficient to prevent iron deficiency anemia.

Dr. Martorell: I would like to return to the issue of iron programs in areas where we have malaria. I think you presented very important research that the delivery of iron in programs matters. For example, providing iron through fortified complementary foods as opposed to supplementation may lead to less free iron. WHO's policy right now is not to do any form of iron intervention. In your conclusions you recommended malaria control along with supplementation. Would you recommend fortified complementary foods in high malaria areas?

Dr. Domellöf: I fully agree with you that iron-fortified foods might be a very good alternative since they have never been connected with adverse effects in malarious regions. I didn't elaborate on that during my speech but if you give one daily dose of iron between meals, which is suggested for iron supplements, then you will have a high peak in serum iron, while if you give iron fortified foods in repeated lower doses during the day, you will not get those high peaks. This might influence the risk for malaria.

Dr. Pe Thet Khin: According to the WHO, the prevalence of iron deficiency anemia in our country is about 60%. As you know, malaria prevention is our top priority, and frequently malaria and iron deficiency anemia coexist. According to the papers published around the year 2000, we stopped giving iron to children, but my colleagues in the district are now complaining. They see more children with malaria and anemic heart failure, and the number of children requiring transfusion is increasing. That's why they are reverting back to iron supplementation. What would be your advice on this matter?

Dr. Domellöf: This connects with some of the previous questions. I would suggest to use either iron-fortified foods or a combination of iron supplements and infection control. However, further studies are urgently needed.

Dr. Rodriguez: In basic pharmacology, one unwanted adverse effect of oral iron treatment is constipation [8], but in your study you mentioned that one of the reasons why it seems to be detrimental is diarrhea. Was diarrhea already present in the subjects before oral iron supplementation or was this a consequence of oral iron supplementation based on the premise that iron can be a nutritive ingredient for some microorganisms.

Dr. Domellöf: Constipation, diarrhea and stomach pain have all been described as side effects of iron. In our recent study, we started the infants on iron supplements at 6 weeks – the worst age for colic – so we expected a lot of problems with real or perceived gastrointestinal side effects. However, we found no difference between iron supplements and placebo with regard to any of these gastrointestinal problems, so I think that clinicians and parents may be overestimating the risk for side effects in young infants.

Dr. Ke: We are dealing with a lot with iron-deficient children, and you rightly pointed out that the high-risk low birthweight babies need early iron supplementation, but how early? The earlier recommendation was to wait for 6 or 8 weeks, and now some people are starting supplementation already at 2 weeks. What is your
recommendation? When shall we start iron supplementation for the low birthweight babies, especially those weighing 1.5–2.5 kg, excluding the very low birthweight babies who may get blood transfusion.

Dr. Domellöf: You can start anywhere between 2 and 6 weeks of age. For the prevention of iron deficiency anemia, supplementation must be started before the infant has doubled his/her birthweight. This means that you should start earlier in the smallest preterms. However, if the infant has received blood transfusions, serum ferritin should be measured, and if it exceeds 300 µg/1, iron supplementation should be delayed.

Dr. Mobarak: I was wondering whether you can comment on iron fortification in areas where thalassemia is very prevalent, especially Bangladesh where the screening is not very good. About 50% of thalassemia patients are not identified or identified very late. If you start fortifying foods with iron, what could be the consequences in areas where thalassemia is very prevalent?

Dr. Domellöf: This highlights my previous point that all anemia is not iron deficiency anemia. It’s important that you perform local studies to assess causes of anemia before you make decisions on iron supplementation programs. With regard to iron-fortified complementary foods, they are likely to be safe and useful in your setting since children with thalassemia have similar iron requirements as other children. The risk for iron overload in thalassemic patients occurs only if you persistently treat their anemia with iron supplements or blood transfusions.

References
