While iron supplementation can correct anemia at any stage, there is little evidence to support the idea that iron supplementation can correct neurodevelopmental deficits caused by iron deprivation in utero or in early childhood

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Iron Nutriture of the Fetus, Neonate, Infant, and Child

by Carla Cerami

Key insights

Iron is an essential nutrient throughout the human life cycle, but particularly for the developing fetus, the neonate, and in early childhood. Before birth, iron needs are met through maternal iron transfer, and after birth, through dietary sources. Breast milk is low in iron, and care should be taken to offer additional sources of iron to breastfed infants. Worldwide, iron deficiency remains one of the most common micronutrient deficiencies in children, affecting an estimated 43% of the global population. Although a child with iron deficiency will continue to grow, depletion of tissue iron stores will cause specific clinical symptoms.

Current knowledge

Iron deficiency during fetal development and the first 2 years of life is associated with poor growth and decreased cognitive, motor, and emotional development. Deficiency of iron during this critical window of development can permanently alter the brain and nervous system. The strongest evidence for the effect on neurological outcomes comes from studies in school-aged children and teenagers with iron deficiency and iron deficiency anemia: modest improvements in cognitive outcomes were obtained after iron supplementation. However, the effects of iron supplementation in infants and young children are less clear.

Practical implications

The fetus obtains its iron via the placenta, and 80% of iron is transferred during the final trimester of pregnancy. However, the clinical benefits of maternal iron supplementation on birth outcomes

Ensuring adequate maternal iron status and offering children a varied diet are important for maintaining iron levels.

require further study. An alternate strategy to improve the infant's iron stores is delayed cord clamping. Full-term, breastfed infants should begin an iron supplement at 4 months, and formula-fed infants should be given iron-enriched formulas. At weaning and beyond, children should be offered a varied diet that includes foods rich in heme and non-heme iron.

Recommended reading

Low M, Farrell A, Biggs B-A, Pasricha S-R: Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. CMAJ 2013;185:E791–E802.

Iron Nutriture of the Fetus, Neonate, Infant, and Child

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Key Messages

- Iron requirements are high in neonates and infants, particularly in premature babies.
- Breast milk is low in iron, and breastfed infants should be offered additional sources of iron.
- Iron deficiency is the most common micronutrient deficiency in children and causes deficits in exercise capacity and neurodevelopment.

Keywords

Iron · Nutrition · Iron deficiency · Infants · Neonates

Abstract

Iron is a key nutrient and is essential for the developing fetus, neonate, infant, and child. Iron requirements are high during early stages of life because it is critically important for the production of new red blood cells and muscle cells as well as brain development. Neonates, infants, and children obtain iron from dietary sources including breast milk (lactoferrin) and heme- and non-heme-containing foods. Iron deficiency (ID) is the most common micronutrient deficiency in children and pregnant women worldwide. ID and iron deficiency anemia (IDA) can affect growth and energy levels as well as motor and cognitive performance in the developing child.

The fetus is completely dependent on maternal iron crossing through the placenta and, although it is generally well protected against deficiency at birth, ID in mothers can increase the risk of ID and IDA in their children as early as 4 months. This review will discuss the uses of iron, iron requirements, and the sources of iron from conception through childhood. In addition, it will describe the prevalence and clinical manifestations of ID and IDA in children and discuss recommendations for iron supplementation of children and pregnant women.

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Introduction

Iron is an essential nutrient during all stages of human development. It has particular importance for children because of its critical impact on their development. In the human body, iron is found mainly in (1) hemoglobin in red blood cells (RBCs) and erythroblasts; (2) myoglobin in muscle cells and in other iron-containing proteins such as cytochromes and catalases (15%); (3) transferrin-bound iron in circulation; (4) storage proteins such as ferritin and hemosiderin. It is essential for DNA replication and many other metabolic processes. By far the biggest use of iron is in the production of new RBCs. However, in infants and children, muscle growth and production of new myoglobin are also important consumers of iron.

Table 1. Definitions of anemia

Population	Hemoglobin, g/dL
Pregnant women	11
Infants	11
Children aged 6 months to <5 years	11
Children aged 5 to <12 years	11.5
Children aged 12 to <15 years	12

Iron status is regulated by intestinal absorption and transport, and there is no controlled mechanism for iron excretion. In adults, dietary iron sources provide only 5% of the daily needs and the remainder is obtained by recycling iron released during the breakdown of old RBCs. In contrast, infants and children must obtain 30% of their daily iron from their diet to provide the necessary iron for new muscle cells and RBCs [1].

Iron deficiency (ID) is the most common micronutrient deficiency in children [2, 3]. Anemia, primarily caused by ID, disproportionately impacts young children and pregnant mothers.

In the US, 7–9% of children ages 1–3 years have ID. However, the worldwide burden is much higher with an estimated 43% globally in 2011 and approximately 70% in Central and West Africa [4]. As will be discussed in more detail below, ID during fetal development and the first 2 years of life is associated with poor growth and decreases in cognitive, motor, and social emotional development [5–7]. Both the United States Department of Health and Human Services and the World Health Organization (WHO) have set goals to reduce ID and iron deficiency anemia (IDA). The WHO priorities have now been adopted as Priority Nutrition Indicators for the United Nation's post-2015 Sustainable Development Goals [8, 9].

Definitions of ID in Early Life

Iron is categorized as a Type 1 nutrient. During ID, as in all Type 1 nutrient deficiencies, a child will continue to grow, but tissue depletion of the nutrient occurs and causes specific clinical symptoms [10]. Routine screening for ID and IDA between 6–24 months is recommended, especially for children living in areas with a high prevalence of ID. The minimum laboratory screen for IDA is hemoglobin and the guidelines outlined in Table 1 can be used to define anemia. In upper-income

countries, a full blood count is obtained, which will give hemoglobin, hematocrit, mean corpuscular volume, and RBC distribution width. In children with IDA, mean corpuscular volume will be decreased and RBC distribution width will most likely be increased. In some settings, ferritin is also measured as part of the screening process. However, ferritin values can be misleading in children living in areas where the infectious disease burden is high because ferritin is also an acute-phase protein.

Effects of ID on Neurodevelopment

The strongest evidence for an effect on neurological outcomes comes from studies done on cognition in school-aged children and teenagers with ID and IDA [11]. A recent meta-analysis in older children and adults showed evidence of a modest improvement in the cognitive domains of concentration, intelligence, memory, psychomotor skills, and scholastic achievement after iron supplementation [12]. The effects of ID and iron supplementation in young children are less clear. Further details are summarized by Pasricha and colleagues [13] in an accompanying paper in this issue.

Children and infants with ID also have decreased psychomotor and mental development, but the timing, degree, and duration of the deficiency may all have profound effects on how and when these symptoms manifest. The brain is not a homogenous organ and different regions of the brain develop more rapidly at different times in development [14]. For example, in the last trimester of pregnancy there is rapid myelination and development of the striatum and the hippocampus. In children between the ages of 6 months and 3 years there is also rapid myelination and the frontal cortex and basal ganglia (motor control) are both developing most rapidly [15]. Infants with ID can have multiple symptoms that are consistent with impaired hippocampal function, reduced myelination, and altered temperament and altered dopamine metabolism. For example, iron-deficient infants can present with decreased attention and memory [16, 17]; deficits in visual and auditory systems [18, 19]; and altered temperament and social and emotional behaviors [20–22]. Taken together, the evidence implies that ID in early life can permanently alter the brain and nervous system and may explain at least in part why little efficacy has been shown on neurodevelopmental outcomes in iron supplementation trials in young children [23–26].

Effects of ID on Immunity and Susceptibility to Infection

Iron has opposing effects on immunity and susceptibility to infection. It can decrease efficacy of and cytokine production by lymphocytes [27, 28], and recent work has shown that it has detrimental effects on the phagocytic activity of macrophages and oxidative burst in neutrophils [29]. On the other hand, ID can be protective against certain infectious diseases including malaria in both children [30–32] and pregnant women [33, 34]. Further information on this is described by Prentice [35] in this issue.

Effects of ID on Exercise Capacity

Iron is an essential element for the transportation of oxygen and is a cofactor for enzymes involved in aerobic metabolism. ID and IDA both impair exercise capacity and increase fatigue [36, 37].

Iron during Fetal Development

Iron is critical for rapidly developing and proliferating cells. During fetal development, iron plays a profound role in organ development, particularly the brain. Evidence suggests that iron is of particular importance to the hippocampus which is rapidly developing during the late stages of gestation [38]. Of course, the region of the brain affected by in utero ID (and therefore subsequent clinical effects observed in the infant) depends on the magnitude of the deficiency and when in pregnancy the deficiency begins. In addition, it is essential for the fetus to acquire adequate iron stores from its mother to sustain growth during the first 6 months of life when the iron intake from breast milk is very low (see below).

The fetus obtains iron from the mother through the placenta and 80% is transferred during the third trimester of pregnancy [39]. Transferrin-bound iron is transferred directly from the maternal blood to the syncytiotrophoblast in the placental villi via transferrin receptor 1 (TFR1). After binding to iron (Fe^{3+}) on the apical side of the syncytiotrophoblast, holotransferrin with its bound iron is internalized and the iron is released into the cytoplasm. The trophoblasts may also take up non-transferrin-bound iron via ZIP8 or ZIP14 [40, 41] and heme iron via LRP1 [42]. No matter which pathway it uses to enter the cell, all non-heme iron is released from the basal side of syncytio-

trophoblast via ferroportin (FPN). It remains unclear how iron is transported across the fetal endothelium and then to fetal transferrin [43], and pathways for heme iron are still not fully described.

The regulation of iron transport from the mother to the fetus across the placenta is thought to be controlled by the fetus for the following reasons: (1) infants of anemic women are usually born with normal iron status [44] and (2) fetal signals of iron status and gestational age can influence expression of TFR1 on the placenta [43]. One molecule which may influence placental iron transport is fetal hepcidin [45], but the role of maternal hepcidin remains unclear [46]. Recent evidence indicates that the placenta upregulates iron (and zinc) transporters in response to maternal deficiency [47].

The prevalence of ID is high during pregnancy, and 43% of pregnant women worldwide are anemic. ID accounts for 50–75% of anemia cases and is thought to be largely due to inadequate diet and increased nutritional requirements during pregnancy [48]. However, inflammation also plays a role by downregulating absorption (see Prentice [35] in this issue). It is general policy for pregnant mothers worldwide to be routinely supplemented with iron [49]. The US Center for Disease Control recommends that all pregnant women take a 30 mg/day iron supplement [50] and the WHO recommends supplementation with 30–60 mg/day [51]. However, the UK takes a very different view. Based on evidence that iron absorption is physiologically upregulated in pregnancy and that cessation of menstruation also reduces iron losses, there is no increase in the recommended nutrient intake for iron and supplements are only recommended if there is

During fetal development, iron plays a profound role in organ development, particularly the brain

evidence of anemia [52]. The clinical benefits of maternal iron supplementation on birth outcomes (including preterm delivery, low birth weight, and neonatal morbid-

ity and mortality) are still unclear despite decades of research [49]. A systematic review in 2015 found that routine iron supplementation reduced maternal IDA at birth (relative risk 0.29, 95% CI 0.17–0.49) but did not have consistent benefits on pregnancy outcome [53]. Part of the problem may be that iron is rarely compared against a true placebo control. Notably, a recent trial from Kenya using true controls reported a robust effect on birth weight with a large benefit in women who were iron deficient [54]. In addition, there is no definitive evidence showing that iron supplementation of nonanemic women improves maternal or infant outcomes. An alternate

strategy recommended by the WHO to improve the infant's body stores of iron is delayed cord clamping after birth [55, 56]. The timing of delayed clamping varies between studies but is generally done between 1 and 5 min after delivery, or at the end of umbilical cord pulsations [57]. This can impart an estimated 80 mL of blood transfer after 1 min and 100 mL by 3 min which will impart an extra 40–500 mg/kg of iron and has been shown to have a significant benefit on ferritin levels in the infant at 6 months [58].

Iron during the Neonatal Period and Early Childhood

At birth most full-term infants have high to normal hemoglobin concentrations (15–17 g/dL) and then remain iron replete until 6 months of life. As noted above, babies of mothers with ID and IDA are at increased risk of ID, but this deficiency develops at 4–6 months and is not apparent at birth. Premature babies have overall greater nutritional needs and higher iron requirements than healthy full-term babies (Table 2) [59]. Premature infants often also have lower iron stores than full-term infants and are at increased risk of developing ID and IDA [60].

There are 3 main dietary sources of iron: breast milk (where iron is bound to lactoferrin), heme iron, and non-heme iron. For neonates and very young infants, the only sources of iron are breast milk and/or formula. The concentration of iron in breast milk is very low and declines over time from 0.6 mg/L at 2 weeks to 0.3 mg/L at 5 months postpartum [62]. (Note that for a 4-kg baby who is likely to consume around 800 mL breast milk its intake would be about one-fifth of the value recommended in Table 2; but see comments below about the high bioavailability.) Current evidence suggests that if a mother has severe anemia, breast milk concentration decreases further, but not if a mother has mild-moderate anemia [63].

The iron in breast milk is highly bioavailable (50% compared to 3–4% in infant formula), although the precise mechanisms of absorption remain unclear [64]. The iron in breast milk is found in iron-binding proteins, predominantly lactoferrin. Lactoferrin is one of the most abundant proteins in milk [64]. It is a single polypeptide chain (MW 75–90K) that can bind 2 molecules of ferric iron [65] and closely resembles transferrin (the iron-carrying protein in serum) [66]. Like transferrin, lactoferrin functions as both an iron carrier molecule and an iron chelator. For example, transferrin in normal human circulation is only 30–40% saturated with iron, which makes

Table 2. Daily iron requirements during childhood [61]

Age	Recommended dietary amount
Full-term	1 mg/kg
Premature	2–4 mg/kg
1- to 3-year-olds	7 mg
4- to 8-year-olds	10 mg
9- to 13-year-olds	8 mg
14- to 18-year-old boys	11 mg
14- to 18-year-old girls	15 mg

over half of its binding sites available to bind excess iron and accounts for its bacteriostatic activity [67]. The extent to which lactoferrin is saturated with iron in breast milk is uncertain (one estimate suggests 10%); however, it is known to possess bacteriostatic properties which are at least in part attributable to its unsaturated iron-binding capabilities [68]. Lactoferrin is most likely absorbed in the small intestine of infants and neonates [69].

As will be discussed in more detail below, while iron supplementation can correct anemia at any stage, there is little evidence to support the idea that iron supplementation can correct neurodevelopmental deficits caused by iron deprivation in utero or in early childhood. Hence, current evidence suggests that it is important to provide a source of iron for children during the first 2 years of life [7, 70, 71]. Both the WHO [72] and the American Academy of Pediatrics [73] recommend exclusive breastfeeding for 6 months. It is recommended that full-term breastfed infants should start an iron supplement at 4 months (elemental iron 1 mg/kg daily, maximum 15 mg) and the supplement should be continued until the infant is taking sufficient quantities of iron-rich complementary foods [1]. If formula is used, full-term infants should be given iron-fortified formulas [74]. Human milk is also the recommended food for preterm babies, but human milk alone does not supply adequate amounts of iron, protein, calcium, phosphorous, and other micronutrients [75]. Hence, human milk fortifiers, iron supplements, and/or specially formulated preterm formula are often recommended [74]. Breastfed premature infants should start an iron supplement at 2 weeks of age and continue until 1 year of age [59, 71].

Full-term and preterm babies should be taking complementary foods by 6 months of age [76, 77]. Iron-rich complementary foods include meat (lamb, chicken, beef, and pork), baby cereals (including fortified rice), and some vegetables (green beans, peas, and spinach) [76, 78].

Iron during Childhood

Iron is obtained entirely from dietary sources; hence, it is important that children are offered a diverse diet with a variety of iron-rich foods in order to provide an adequate intake of iron (Table 2). Children who do not eat at least 3 servings of iron-rich foods/day may benefit from an iron supplement [1]. Heme iron is the most bioavailable form of iron and is readily absorbed from meat, poultry, and fish. Non-heme iron is available from vegetables (especially spinach, lentils, and pumpkin seeds) and fortified cereals. Fortified cereals are the major source of iron for most children in the United States [79]. Other important sources of non-heme iron include beans (kidney, lima, and navy beans) and nuts. Absorption of non-heme iron is increased by foods rich in vitamin C (oranges, grapefruit, broccoli, tomatoes) and decreased by phytate (in bran, oats, and rye fiber), polyphenols (in tea, coffee, and cocoa), dietary calcium, and soy proteins. Calcium inhibits the absorption of iron by as much as 60% and thus there is a risk of ID in children who drink more than 700 mL of cow's milk per day [50].

Conclusions

Iron requirements are high during all stages of human development. ID and IDA result in deficits in growth, neurological development, exercise capacity, and immune function. The recommended dietary allowances

(RDA) are 1 mg/kg for full-term infants, 2–4 mg/kg for premature infants, 7 mg for 1- to 3-year-olds, 10 mg for 4- to 8-year-olds, and 9–13 mg for 9- to 13-year-olds. Iron sources include lactoferrin in breast milk as well as heme and non-heme iron from other dietary sources. Iron supplementation should be implemented if a child has a low hemoglobin level, does not have access to 3–4 servings per day of iron-rich foods, or lives in an area with a high prevalence of ID.

It is important that children are offered a diverse diet with a variety of iron-rich foods in order to provide an adequate intake of iron

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