Setting the Stage for Child Health and Development: Prevention of Iron Deficiency in Early Infancy¹,²

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Abstract
Iron deficiency is estimated to be the most common nutritional deficiency worldwide and is particularly persistent among infants and children. The high prevalence of anemia in 6- to 9-mo-old children raises the concern that birth iron stores in some infants are inadequate to sustain growth and development through the first 6 mo of life, and postnatal factors are contributing to early depletion of iron stores and development of anemia. At the same time, there are concerns about negative effects of excess iron in infants. Maternal iron status, infant birth weight and gestational age, as well as the timing of umbilical cord clamping at birth all contribute to the establishment of adequate total body iron at birth. Postnatally, feeding practices and growth rate are factors that will affect how quickly birth iron is depleted during the first 6 mo of life. Under conditions in which maternal iron status, birth weight, gestational age, and umbilical cord clamping time are optimal, and exclusive breast-feeding is practiced, infants should have adequate iron stores for the first 6–8 mo of life. Under suboptimal conditions, infants may not reach this goal and may need to be targeted for iron supplementation before 6 mo of age.  J. Nutr. 138: 2529–2533, 2008.

Introduction
As presented in this symposium, iron deficiency (ID)³ during infancy and young childhood is a particularly prevalent and persistent problem (1) with serious negative and potentially irreversible effects (even after treatment) on development (2). Avoiding negative effects of ID will require a preventative approach, which begins prenatally and continues throughout infancy and early childhood, to ensure and maintain adequate iron status during infancy. This brief article addresses the factors most important for prevention of ID during the first 6 mo of life and also discusses whether, when these factors are optimized, adequate iron status during early infancy can be ensured.

Ensuring adequate iron status at birth: prenatal factors
During gestation, iron is actively transported across the placenta from the maternal to fetal circulation (3). This active transport of iron is necessary for the high production of red blood cells occurring throughout gestation, marked by the steadily increasing fetal hemoglobin concentration as gestation nears term. The large fetal red cell mass is needed to provide sufficient oxygen for development as well as to overcome the relatively hypoxic uterine environment. Although all of the steps of iron transport across the placenta have not been completely elucidated, it is generally believed that transferrin-bound iron in the maternal circulation is taken up by the placenta via transferrin receptors (TfR) on the placental brush border membrane (3). The transferrin-TfR complex is then internalized into the placenta via coated vesicles, which are later acidified, releasing the iron from transferrin into the cytosol via a process thought to be partially regulated by divalent metal transporter-1 (DMT1). Iron is then transferred out of the cell into circulating fetal transferrin in a process likely involving ferroportin-1 (FPN1) and placental copper oxidase (4).

The active transport of iron across the placenta ensures that healthy infants born at term with adequate birth weight will generally have high total body iron at birth, both in circulation and in stores. In healthy, term infants, the amount of total body iron is estimated to be ~75 mg/kg body weight (5); for comparison, the iron content of an adult male is ~55 mg/kg body weight (6). Newborns have the highest hemoglobin levels at any time during life: ~170 g/L. Hemoglobin constitutes ~70% of their total body iron, and the other large portion, ~25%, is stored in ferritin (7).

During the first months of infancy, as the infant adapts to the extraterine environment, dynamic hematological changes oc-
The high hemoglobin concentration seen at birth, which was important for adequate oxygen delivery in utero, is no longer needed, and red blood cell production slows in response to the greater oxygen availability outside of the womb. Combined with the shorter life span of fetal red blood cells, these 2 factors result in a decrease in hemoglobin concentration. The heme iron recycled from senescent red blood cells is stored in ferritin. Thus, the iron reserves present at birth, as well as the recycled heme iron added to reserves during this period of redistribution, will form the main source of iron during the first several months of life.

**Maternal iron status.** Many studies have examined the relation between iron and/or hematological status in the mother during pregnancy and those in the infant, both at the moment of birth and longitudinally. Preconceptional iron status may also be a potentially important factor; in 1 study of pregnant rhesus monkeys, infant iron status at birth (and through 6 mo of age) reflected the mother’s iron status at conception, regardless of whether she had been provided with an iron-adequate diet during pregnancy (8).

In the presence of ID during pregnancy, there are some “protective” mechanisms that attempt to maximize iron transfer to the fetus. At the maternal level, iron absorption increases throughout pregnancy (9), and ID will further increase absorption, so more iron is available to the fetus. At the level of the placenta, expression of placental transport proteins for iron increases during ID (4), allowing a greater transport of iron to the fetus. A prenatal iron and zinc supplementation study in Peru showed that transfer of an oral dose of stable iron isotope to the fetus was greater in mothers with ID than in iron-replete mothers (10). In the study, the cord blood of infants born to mothers with the lowest ferritin levels had the highest levels of the stable isotope.

The extent to which these mechanisms “protect” the infant from maternal ID has been a matter of debate. Cross-sectional studies that assessed the relation between iron or hematological status in cord blood and maternal iron or hematological status at delivery have produced conflicting results, likely for various reasons including the extent of ID in the women studied (deficient vs. sufficient) and the physiological background of pregnancy and delivery (e.g., maternal plasma dilution, the hypoxic uterine environment, and inflammation accompanying delivery), which affects commonly used indicators such as hemoglobin and ferritin, making their interpretation challenging around this time.

Results from several longitudinal studies, however, support the idea that ID and iron-deficiency anemia (IDA) during pregnancy can affect fetal iron accretion enough to have long-term effects (11–14); interestingly, some of these studies showed no effect of maternal status on infant iron status/hematological indicators at birth (12,14). In a sample of mothers and infants from Zimbabwe in which total body iron at birth was calculated as the sum of iron in ferritin and hemoglobin, maternal hemoglobin during pregnancy was positively associated with infant body iron at birth, such that infants of mothers with the lowest hemoglobin concentrations had the lowest total body iron at birth (15). As a result, these infants were at greatest risk of anemia between 3 and 12 mo of age. Three studies, from Spain, Jordan, and Indonesia (11–13), demonstrated a higher incidence of ID or IDA in infants born to mothers with IDA during pregnancy, as compared with infants born to mothers with adequate iron status (Fig. 1). A randomized controlled trial from Niger (14), one of the few prenatal iron supplementation trials to follow infant outcomes past the neonatal period, showed that infants born to mothers who had received iron supplementation during pregnancy had a lower incidence of ID at both 6 and 9 mo of age.

**Birth size and gestational age.** Apart from maternal iron status, the size of the infant will also determine the size of iron stores at birth. The linear relation between body iron and birth weight was first established in 1951 by assessing whole-body iron content (estimated to be 75 mg/kg body weight) in aborted and stillborn fetuses (5). Gestational age is also correlated to the size of body iron stores at birth, although likely via overall birth size. Liver iron concentration remains relatively constant throughout gestation (16), but during the last 8 wk of gestation, there is an increase in the total amount of liver iron because of an increase in liver size, which is related to birth size. Few studies have directly measured body iron content in the newborn, and it is possible that the conditions that caused fetal death in these studies could have affected body iron content; however, the estimated total body iron at birth calculated in the study of Zimbabwean infants was comparable to the direct assessment made from the study in 1951 (15).

**Maintaining adequate infant iron status: perinatal factors.** Delaying the time at which the umbilical cord is clamped after birth by ~2–3 min will allow a “redistribution” of blood between the placenta and newborn, favoring a “placental transfusion” to the infant: ~35–40 mL/kg body weight is provided to the infant, which for a ~3-kg infant, represents 75 mg of iron as hemoglobin, or ~3 mo worth of infant iron requirements (17). Conversely, immediately clamping the umbilical cord (i.e., within 10–15 s of delivery) will deprive the infant of a substantial portion of birth body iron.

The beneficial effect of delayed cord clamping on infant iron and hematological status has been demonstrated through 6 mo of age (18). In a randomized controlled trial, the difference in storage iron at 6 mo of age between early- and delayed-clamped infants was the equivalent of ~1.25 mo worth of iron requirements (19). This difference was even larger among infants starting out life with compromised iron status, including infants...
born to mothers with ID during pregnancy and infants with birth weight between 2500 and 3000 g.

**Maintaining adequate infant iron status: postnatal factors**

In the postnatal period, how quickly birth body iron is utilized will depend on the infant's rate of growth, iron intake, and iron losses. Infant sex is another factor that appears to affect the development of ID, although the exact mechanisms are not yet understood.

**Growth.** The main iron requirements for growth include blood volume expansion and gain in lean body mass. As the infant grows and blood volume expands, an increased amount of iron will be needed in hemoglobin, and infants with greater weight gain are more at risk for ID (20,21). For a ~3.2-kg infant at birth, who will weigh ~7.6 kg by 6 mo of age, the needed increase in hemoglobin iron is ~92 mg (17). Increased lean body mass will also require iron for both myoglobin and enzymes, which is estimated to be ~20% of hemoglobin iron (6). Thus, low-birth-weight infants are at increased risk of ID not only because they start out life with smaller iron stores but also because of their faster rate of postnatal growth (7).

**Iron intake.** For the first 6 mo of life, infants who are exclusively breast-fed have low iron intake, as human milk is not high in iron. Assuming a human milk intake of ~0.78 L/d, and an average iron content of 0.35 mg/L, the average breast-fed infant will ingest ~0.27 mg of iron. Assuming a range of absorption between 12 and 56%, ~0.03 to 0.15 mg of iron will be absorbed per day (17). Differences in techniques (e.g., radioisotopes (22,23) vs. stable isotopes (24,25)), infant age, and infant iron status all contribute to the variability in estimates of iron absorption in infants. Iron absorption appears to go through developmental changes throughout infancy. In adults, there is an inverse relation between iron absorption and iron status that is regulated at the level of the intestine by several different factors: recent dietary iron intake (the "dietary regulator"), iron stores (the "stores regulator"), and erythropoietic activity (the "erythropoietic regulator") (26). These "regulators" may not be functioning at the same level in young infants. In an iron-supplementation study of 4- to 9-mo-old infants in Honduras and Sweden, there was a universal positive hemoglobin response to iron supplementation at 4 mo of age, independent of initial hemoglobin or iron status (27). At 6 mo of age, however, the hemoglobin response to iron supplementation was dependent on initial iron status. Similarly, a study of intestinal DMT1 and FPN1 expression in rat pups showed that expression increased with age and that at earlier ages, expression was not down-regulated by iron supplementation, as it was at later ages (28). Infant iron status may also affect estimates of human milk iron absorption. Peruvian infants (6–9 mo of age) with low ferritin concentration absorbed significantly more iron from human milk compared with infants with normal ferritin (56 vs. 38%, P = 0.04) (29). These combined results may indicate that infants with low iron stores or low recent dietary intake may be able to up-regulate iron absorption to compensate for ID, but, especially at younger ages, infants may not be as effective at down-regulating iron absorption. This could explain some of the negative results seen when iron supplementation is provided to iron-replete infants (30), a topic addressed later in this supplement (31).

Although the estimated amount of iron absorbed from human milk is low, exclusive breast-feeding is thought to be protective of infant iron status in areas where iron-fortified foods are not common. In a study of Zambian infants, where over 50% had developed IDA by 6 mo of age, exclusive breast-feeding at 4 mo was protective of iron status compared with infants receiving early complementary foods (32). Iron from other complementary foods or liquids will not be as well absorbed, and these foods can interfere with the absorption of human milk iron (33).

**Iron losses.** Because there is no excretion pathway for iron from the body, iron is normally lost via sloughing of epithelial cells of the gastrointestinal tract (which are eliminated through feces and urine) and the skin. It is estimated that, in total, those losses will amount to ~0.18 mg/d (17) for a breast-fed infant, which is roughly equivalent to the amount of iron absorbed from human milk, assuming the highest level of absorption. That breast milk iron intake will likely only recoup normal iron losses reemphasizes the importance of adequate birth body iron for preventing ID during early infancy.

During the first 6 mo of life, there should be few causes of pathological iron loss, other than the use of cow’s milk, which, in addition to being a poor source of iron, can cause small intestinal blood loss, an effect that appears to be greater in earlier infancy than later (34). Before 6 mo of age, the role of intestinal helminths (such as hookworm) in causing blood, and thus iron, loss is thought to be minimal. Diarrhea, unless accompanied by blood loss, is also thought to have a minimal effect on iron status.

**Other factors: infant sex.** Several studies have shown that male infants tend to be more susceptible to ID than female infants even after controlling for differences between the sexes in growth rate and diet. From an iron-supplementation study in Honduras and Sweden, the percentage of males with IDA at 9 mo of age was significantly higher than the percentage of females with IDA; at 4 and 6 mo of age, some indices responded to iron supplementation (hemoglobin and TIR), but others did not (mean corpuscular volume, zinc protoporphyrin, and ferritin), perhaps indicating that the latter indices are physiologically different between the sexes rather than being caused by greater ID among males (35). Lower ferritin concentrations among boys were also observed at 6 mo of age in an observational study of children in Norway (36). In that study, boys were more likely to have low cord blood ferritin (and higher cord TIR) at birth than girls, which was positively correlated with ferritin levels at 6, 12, and 24 mo of age. Sex differences in ferritin in cord blood through-out gestation have been previously reported (37). Postnatally, additional proposed mechanisms for the disparity in iron indices between males and females include differences in iron metabolism during infancy (e.g., differences in absorption or losses), body composition (e.g., lean vs. fat mass), and hormonal influences.

**ID and anemia during early infancy**

As presented earlier in this symposium, in many countries, the prevalence of anemia (hemoglobin <110 g/L) between 6 and 9 mo of age is alarmingly high: 64–93% in sub-Saharan Africa, 70–85% in Southeast Asia, and 59–75% in Latin America and the Caribbean. Even if a more conservative estimate of anemia (<105 g/L) is used (38), the prevalence of anemia remains between 24 and 67% among 6- to 9-mo-old children in 6 countries from Latin America and the Caribbean (1). It is important to note that not all anemia in this age group will be attributable to ID. Roughly half of anemia is estimated to be IDA (39), but results from some recent studies have questioned...
whether this assumption is applicable to all age groups and settings (40), and the appropriate cutoff to define anemia, particularly in infants, is still a matter of debate (38). Nevertheless, because of the high iron needs during infancy, the high levels of ID and IDA in mothers in the developing world, combined with frequent low birth weight and poor infant feeding practices, it is reasonable to assume that a proportion of anemia in early infancy will be caused by ID. Whether adequate iron status will be maintained through at least the first 6 mo of life will depend on whether pre-, peri-, and postnatal factors, such as birth weight and cord-clamping time, are "optimized" (Fig. 2); although limitations exist for theoretical calculations, it does appear that under optimal conditions, adequate iron status among infants can be maintained through at least 6 mo of age (17).

It is important to clarify, however, that even for infants at low risk of becoming iron deficient before 6 mo of age, iron requirements remain high from ~6 mo of age through the end of y 2 of life. The recommended iron intakes set by the U.S. Institute of Medicine are ~11 mg/d between 6 and 12 mo and 7 mg/d between 12 and 24 mo (41); thus, a highly bioavailable source of iron will be required to meet those needs.

The challenge of “high-risk” infants

Infants at risk of developing ID before 6 mo of age include preterm, lower-birth-weight infants, those who receive early cord clamping, and those born to mothers with poor prenatal iron status. These “at-risk” infants may present a challenge because of the financial, cultural, and logistical difficulties involved in identifying them, assessing their iron status before 6 mo of age, and providing targeted iron supplementation. Thus, focusing on preventing these risks (e.g., improving maternal nutrition, changing delivery care practices, improving infant feeding practices) so that targeting before 6 mo of age is no longer necessary, should be the ultimate goal. The additional research needs for targeting “high-risk” infants, as well as scaling up interventions we know are efficacious, are outlined by Stolzus in this symposium (42).

Other articles in this symposium include references (1,2,31,42).

Literature Cited


