Iron in fetal and neonatal nutrition

Raghavendra Rao[a,*] and **Michael K. Georgieff**[a,b]

a *Division of Neonatology, Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA*

b *Institute of Child Development, Center for Neurobehavioral Development, University of Minnesota, Minneapolis, MN, USA*

Summary

Both iron deficiency and iron excess during the fetal and neonatal period bode poorly for developing organ systems. Maternal conditions such as iron deficiency, diabetes mellitus, hypertension and smoking, and preterm birth are the common causes of perinatal iron deficiency. Long-term neurodevelopmental impairments and predisposition to future iron deficiency that are prevalent in infants with perinatal iron deficiency require early diagnosis, optimal treatment and adequate follow-up of infants at risk for the condition. However, due to the potential for oxidant-mediated tissue injury, iron overload should be avoided in the perinatal period, especially in preterm infants.

Keywords

Infant; Iron deficiency; Iron overload; Iron; Newborn

Introduction

Iron and iron-containing compounds play vital roles in cellular function in all organ systems. The requirement for iron is greater in rapidly growing and differentiating cells. Iron deficiency during the fetal and neonatal (perinatal) period can result in dysfunction of multiple organ systems, some of which might not recover despite iron rehabilitation. However, the presence of excess iron during the perinatal period can also be detrimental to developing organs. Preterm infants with immature antioxidant systems are particularly vulnerable. Maintaining iron homeostasis that avoids both iron deficiency and toxicity is essential for optimal development and function. This paper discusses the iron balance in the fetus and the neonate, the clinical spectrum of iron deficiency and iron overload disorders during this period, their pathophysiology and current management strategies.

Determinants of iron status in the fetus and neonate

The total body iron content of a newborn infant born during the third trimester is approximately 75 mg/kg; approximately 60% of this is accreted during the third trimester of gestation.[1] The distribution of the body iron is 75–80% in red blood cells (RBC) as hemoglobin (Hb), approximately 10% in tissues as iron-containing proteins (e.g. myoglobin and cytochromes), and the remaining 10–15% as storage iron (e.g. ferritin and hemosiderin). The storage iron

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*Corresponding author. Mayo Medical Code 39, 420 Delaware Street SE, Minneapolis, MN 55455, USA. Tel.: +1 612 626 0644; fax: +1 612 624 8176. *E-mail address:* raoxx017@umn.edu (R. Rao).

content progressively increases and is reflected by cord serum ferritin concentrations >60 μg/L at full term.

The iron requirements after birth are influenced by the time of onset of postnatal erythropoiesis and the rate of body growth. The iron endowment at birth and iron from external, usually dietary, sources meet this need. The period soon after birth is characterized by a 30–50% decrease in Hb secondary to cessation of erythropoiesis, lysis of senescent fetal RBC and expansion of the vascular volume. During this 'physiologic anemia' the Hb can reach 100–110 g/L between 6 and 8 weeks of age. In preterm infants, the Hb nadir can be as low as 60–80 g/L, occur 1–4 weeks earlier than full-term infants and is called 'anemia of prematurity'. An element of disordered or ineffective erythropoiesis might contribute to the earlier, more severe Hb nadir in preterm infants. The iron released during lysis of senescent RBCs (3.47 mg/g of Hb) is stored for future use and is reflected by a transient increase in serum ferritin concentration during the first month of life.[2] In full-term infants, this stored iron supports the iron needs of the ensuing erythropoiesis and growth until 4–6 months of age. In preterm infants, earlier iron supplementation is necessary (see below).

Common factors that affect iron homeostasis during the perinatal period are listed in Box 1. As with other age groups, iron deficiency is more common than iron excess.

Perinatal iron-deficiency conditions

Certain gestational conditions associated with decreased fetal iron delivery and/or increased fetal iron demand beyond the placental transport capacity can result in perinatal iron deficiency. As in other ages, available iron is prioritized to support erythropoiesis in perinatal iron deficiency. When maternal–fetal iron delivery is inadequate for this purpose, depletion of storage and non-storage tissue iron occurs.

The prevalence of iron deficiency is greater in women of reproductive age, even in developed countries. Pregnancy requires approximately 1000 mg of additional iron to support the expanding maternal RBC and plasma volumes and the growth of the fetal–placental unit.[3,4] Maternal iron deficiency affects 30–50% of pregnancies[3,5,6] and is the most common cause of perinatal iron deficiency worldwide. More than 80% of pregnant women in developing countries are estimated to be affected.[6] In addition to inadequate dietary iron intake, iron loss due to parasitic infestations, chronic gastrointestinal hemorrhage and high dietary fiber content contribute to iron deficiency in these mothers. In the United States, iron-deficiency anemia has been demonstrated in 27% of pregnant ethnic minority women during the third trimester.[3] Teenagers, recent immigrants from developing countries, women from socially disadvantaged populations and multiparous women with short interpregnancy intervals are particularly affected. Despite iron supplementation, 30% of pregnant women have a low serum ferritin concentration at the end of pregnancy.[7]

Maternal iron deficiency, with or without associated anemia, adversely affects fetal iron status. A maternal Hb concentration <85 g/L is associated with decreased fetal iron stores (cord serum ferritin <60 μg/L). More severe maternal anemia (Hb <60 g/L) is associated with lower cord Hb concentration, as well as cord serum ferritin concentration <30 μg/L, a level suggestive of severe depletion of storage iron and potential brain iron deficiency (see below).[8] A maternal ferritin concentration <12 μg/L appears to be the threshold below which fetal iron accretion is affected[6]; 14% of full-term infants born to iron-deficient mothers have a serum ferritin concentration <30 μg/L at birth. Finally, even when iron endowment appears to be adequate at birth, infants of mothers with mild to moderate iron deficiency anemia are at risk for iron deficiency throughout infancy, especially between 6 and 12 months of age.[5,9]

Box 1: Factors that influence body iron status during the perinatal period.

Factors that have a negative effect:

- Maternal iron deficiency
- Maternal diabetes mellitus
- Maternal smoking
- Intrauterine growth restriction
- Multiple gestation[a]
- Preterm birth
- Acute and chronic fetal hemorrhage, e.g. umbilical cord accidents and fetofetal (donor twin) transfusions
- Immediate clamping of the umbilical cord after birth
- Exchange transfusion
- Restrictive transfusion practice[b]
- Uncompensated phlebotomy losses[b]
- Recombinant erythropoietin use[b]
- Delayed and inadequate iron supplementation[b]
- Exclusive breast milk use[bc]
- Ingestion of cow's milk

Factors that have a positive effect:

- Maternal iron supplement[d]
- Fetofetal transfusion (recipient twin)
- Delayed clamping of the umbilical cord
- Liberal transfusion practice[b]
- Early and adequate iron supplementation[b]
- Use of iron-fortified formula[b]

[a]Iron deficiency is more likely if mother is iron deficient during pregnancy.

[b]The risk of iron deficiency is greater in preterm infants than full-term infants.

[c]Exclusive breastfeeding meets the iron needs of full-term infants during the first 4–6 months of life.

[d]Routine iron supplementation of mothers with adequate iron stores is controversial.

Intrauterine growth restriction (IUGR), maternal smoking and poorly controlled diabetes mellitus during pregnancy are important causes of perinatal iron deficiency in developed countries. All three gestational conditions are characterized by intrauterine fetal hypoxia and augmented erythropoiesis that requires additional iron. Approximately 10% of all pregnancies are complicated by IUGR. Whereas maternal malnutrition is likely responsible in developing countries, pre-existing or pregnancy-induced maternal hypertension is responsible for IUGR in developed countries. In pregnancies associated with IUGR due to maternal hypertension,

placental iron transport is decreased due to placental vascular disease and impaired uteroplacental blood flow. Approximately 50% of IUGR infants are iron deficient at birth, as suggested by cord serum ferritin concentration <60 μg/L.[10] The liver and brain iron concentrations are decreased in IUGR infants without a significant effect on Hb at birth. In severe cases, brain iron concentration could be decreased by 33%.[11]

Maternal smoking during gestation is associated with fetal hypoxia due to carbon monoxide and decreased uteroplacental blood flow due to nicotine and catecholamine-induced vasoconstriction. The augmented erythropoiesis stimulated by fetal hypoxia results in depletion of iron stores in the offspring of these mothers.[12-14] Cord Hb is increased and ferritin concentrations in cord blood and the placenta are decreased 40% and 20%, respectively, in infants of mothers who smoked during pregnancy.[12] To our knowledge, the tissue iron concentration in this infant population has not been assessed.

Between 5% and 10% of pregnancies are complicated by maternal diabetes mellitus. Poorly controlled diabetes mellitus during gestation is associated with maternal and fetal hyperglycemia, fetal hyperinsulinemia, increased fetal metabolic rate and oxygen consumption. The increased fetal oxygen consumption in a relatively hypoxic intrauterine environment stimulates erythropoiesis and expands the fetal RBC mass. The additional iron required for the augmented erythropoiesis cannot be met by increasing maternal–fetal transport. Whereas placental transferrin receptor expression is increased in pregnancies complicated by diabetes mellitus, the affinity of the receptor to maternal transferrin is decreased, probably due to hyperglycosylation of the oligosaccharides present in the binding domain.[15] Furthermore, placental vascular disease might be present in mothers with longstanding, poorly controlled diabetes mellitus, further limiting iron transport across the placenta. Tissue iron is depleted to support the iron needs of augmented erythropoiesis under these situations. Nearly 65% of infants of diabetic mothers (IDM) have perinatal iron deficiency, as suggested by cord serum ferritin concentration <60 μg/L. In approximately 25% of these infants cord serum ferritin is <35 μg/L, suggesting significant depletion of tissue iron, including brain iron.[16,17]

Preterm birth is another important cause of iron deficiency during the perinatal period. Between 25% and 85% of preterm infants with a birth weight <1500 g are at risk of iron deficiency during infancy, depending on their diet and iron supplementation.[18] Preterm birth deprives the fetus of the significant iron accretion that occurs beyond 32 weeks of gestation. The total body and tissue iron contents, Hb and serum ferritin concentration are lower in the preterm infant.[2,19,20] Early onset of postnatal erythropoiesis, greater postnatal growth velocity, uncompensated phlebotomy losses, exclusive use of breast milk and delayed or inadequate iron supplementation predispose the preterm infant to iron deficiency until 24 months of age. Birth weight <1000 g (extremely low birth weight, ELBW), associated IUGR and use of recombinant human erythropoietin (rHuEpo) without adequate iron supplementation are additional risk factors. Without an external source of iron, iron stores in non-transfused preterm infants will sustain effective erythropoiesis only until they have doubled their birth weight, i.e. until approximately 2 months of age.[21] Without iron supplementation, ELBW infants might be in negative iron balance during the first month.[22]

Effects of perinatal iron deficiency

The most well-described effect of iron deficiency is anemia. However, anemia as a consequence of iron deficiency is extremely rare during the perinatal period. Before the appearance of anemia, the storage form of iron in the reticuloendothelial system, specifically in the placenta and liver, is depleted, followed by decreased tissue iron in the heart and brain. Autopsy studies have demonstrated that liver iron is decreased by 90%, heart iron by 55% and brain iron by 40% in infants of mothers with poorly controlled diabetes mellitus.[17] Serum

ferritin concentration <35 μg/L at birth suggest a >70% decrease of storage pools in the liver and the likelihood of brain iron deficiency (see Siddappa et al.[23] for details). Such low serum ferritin concentrations at birth are present in approximately 25% of IDM and 14% of infants born to mothers with iron deficiency.[6,16]

Perinatal iron deficiency adversely affects the growth and functioning of multiple organ systems, including heart, skeletal muscle, the gastrointestinal tract and brain.[24-27] Altered immune function and temperature instability are also attributed to perinatal iron deficiency. [28] The most significant adverse effects of perinatal iron deficiency are neurodevelopmental impairments and predisposition to earlier onset of postnatal iron deficiency.

Effects of perinatal iron deficiency on neurodevelopment—Iron deficiency between 6 and 24 months of age is associated with long-term neurocognitive abnormalities that are not reversed, despite adequate iron supplementation.[29] Iron is essential for neurotransmission, energy metabolism and myelination in the developing brain. The exact mechanisms through which iron deficiency affects brain development and function are not completely understood, although both direct and indirect mechanisms have been proposed.[29]

Iron deficiency during the perinatal period also appears to be detrimental to the developing brain. Research from our laboratory has demonstrated neurometabolic, structural, electrophysiological and behavioral alterations in developing rats subjected to perinatal iron deficiency.[30-32] Brain regions involved with cognitive processing, such as the hippocampus and striatum, appear to be particularly vulnerable. Although iron rehabilitation corrects some deficits, structural and functional abnormalities persist into adulthood.

In contrast to the literature on postnatal iron deficiency, few studies have assessed the role of perinatal iron deficiency on neurodevelopment in human infants. Newborn infants with low cord blood Hb and iron have altered temperament during the first week of life.[33] Preterm infants with iron-deficiency anemia have abnormal reflexes at 36 weeks postconceptional age. [34] Electrophysiological studies from our laboratory have demonstrated that IDM with serum ferritin concentration <35 μg/L at birth have abnormal recognition memory processing soon after birth,[23] which persists in infancy,[35] despite complete repletion of iron stores by 9 months. [36] Tamura et al.[37] have described impaired language ability, fine-motor skills and tractability at 5 years in children born with cord serum ferritin concentration <76 μg/L. Thus, perinatal iron deficiency appears to have immediate and long-term adverse effect on neurodevelopment.

Predisposition to future iron deficiency—Infants with perinatal iron deficiency are at risk of iron deficiency during infancy. Use of cow's milk and inadequate iron supplementation can increase the risk. In developing countries, full-term infants with lower Hb and serum ferritin concentration at birth are at risk of developing iron deficiency at 6 months of age—3 months earlier than those with adequate iron endowment at birth.[5] Even in developed countries, full-term infants with low cord ferritin concentrations have low serum ferritin concentration at 9 months of age.[36] Infants born to mothers who smoked during gestation are at risk for iron deficiency at 12 and 24 months.[38] However, whether these infants had poor iron endowment at birth is not known. Finally, preterm birth as a risk factor for postnatal iron deficiency has been discussed above.

Perinatal conditions associated with iron excess

Certain congenital and iatrogenic conditions are associated with excessive tissue iron deposition during the perinatal period.

Neonatal hemochromatosis is a congenital condition characterized by severe liver injury with iron deposition in intrahepatic and extrahepatic tissues, such as the exocrine pancreas, myocardium, mucosal glands of the oropharynx, and the thyroid[39]; the reticuloendothelial system is spared. Neonatal hemochromatosis is a distinct disorder from adult-onset and juvenile-onset hemochromatosis.[40] The etiopathogenesis of the condition is not completely known. Abnormal fetoplacental iron homeostasis, fetal liver injury, maternal autoimmune disorders and an autosomal recessive transmission have been considered. It has also been postulated that the condition might be an alloimmune disorder.[39]

Neonatal hemochromatosis begins during the fetal period and is often characterized by IUGR, oligohydramnios and preterm birth. The presenting features are acute hepato-cellular failure and multiorgan failure that mimics neonatal sepsis. Serum aminotransferase concentrations are modestly elevated, whereas concentration of alpha-fetoprotein is markedly increased. Iron indices are abnormal with increased serum ferritin concentrations (>800 µg/L; range 1200–40,000 µg/L), hypotransferrinemia and hypersaturation of transferrin. The prognosis is poor; death occurs within weeks in the majority.[39,41]

Multiple RBC transfusions could potentially result in iron excess during the perinatal period. Preterm infants who have received multiple RBC transfusions have increased serum ferritin (>500 µg/L) and liver iron (>40 µmol/g, a value that reflects iron overload in adults) concentrations.[42-44] Iron overload also potentially results from excessive enteral dietary iron supplementation,[45] but has yet to be demonstrated in human infants.

Effects of iron excess during the perinatal period

Full-term infants with high cord serum ferritin concentrations are at greater risk for lower full-scale intelligence quotient at 5 years of age.[37] However, it is not clear whether fetal iron load was responsible for the increased cord serum ferritin in them. Accumulation of protein-bound iron (ferritin and hemosiderin) is not harmful to the tissues per se; it is increased non-protein-bound iron (NPBI), which promotes the generation of reactive oxygen species, that is responsible for the organ dysfunction in iron overload conditions. Because of their poorly developed antioxidant systems, preterm infants are particularly vulnerable. It has been postulated that iron-mediated oxidant stress plays a role in common perinatal conditions, such as bronchopulmonary dysplasia and retinopathy of prematurity. An increased concentration of NPBI and decreased antioxidant defenses have been demonstrated after RBC transfusions in preterm infants.[46] Approximately 25% of full-term infants undergoing cardiopulmonary bypass exhibit evidence of iron overload during and after cardiopulmonary bypass, due to potential hemolysis during the procedure.[47] Finally, it is not known whether enteral iron supplementation could result in oxidative stress during the perinatal period. Iron supplementation in doses as high as 12 µg/kg per day is not associated with evidence of oxidative stress in stable preterm infants.[48] However, ELBW infants, who have poorly regulated iron absorption during the first month of life,[22] might be at risk for iron overload. Developing mice that were fed a formula with iron content similar to that used in human infants (12 µg/L) develop neurodegeneration in the midbrain.[45]

Management of perinatal iron-deficiency conditions

Avoidance of iron deficiency during pregnancy assures optimal perinatal iron nutrition. Accordingly, all pregnant women should be screened for iron deficiency, preferably before pregnancy. Universal screening of infants at birth is not recommended unless they are considered at risk for iron deficiency.

Screening for perinatal iron deficiency

No single, currently available laboratory test will assess iron status in all compartments (RBC, transport, functional and storage). Assessment is further complicated in preterm infants because normative values do not exist for many tests.

Decreased Hb and mean corpuscular volume, and wider RBC distribution width (RDW) used for diagnosing iron deficiency in older age groups[49] are not helpful in the newborn. These are late signs of iron deficiency and do not accurately reflect the iron status of the tissues. For example, despite depleted tissue iron stores, IDM and IUGR infants can have normal or higher Hb because of the preferential routing of limited amount of iron into fetal RBC mass.

Free erythrocyte protoporphyrin and zinc protoporphyrin (ZnPP), either alone or as a ratio of hemoglobin (ZnPP/H), is increased when iron supply is insufficient to support erythropoiesis. The ZnPP:H ratio varies inversely with gestation, and gestation-specific normative values are available.[50,51] Levels are increased in conditions that are associated with fetal hypoxia and perinatal iron deficiency, such as IDM, IUGR and maternal smoking. Despite these observations, it is not clear whether increased ZnPP:H at birth represents the normally occurring, enhanced intrauterine erythropoiesis or perinatal iron deficiency.[52] Finally, ZnPP:H is also increased in other conditions at birth, such as in maternal chorioamnionitis.[50]

Measurement of serum transferrin receptor (sTfR), a truncated form of membrane transferrin receptor (TfR), has been used to assess iron status during the perinatal period. Increased sTfR or its ratio to log-serum ferritin (TfRF index) reflects tissue iron deficiency in children and adults. Cord blood sTfR levels vary inversely with gestational age and are higher in maternal iron deficiency and smoking.[53,54] However, as with ZnPP:H, it is not known whether sTfR or the TfR-F index are reliable measures of tissue iron deficiency or a reflection of the enhanced erythropoiesis during the perinatal period.[55] Ferritin is the major form of storage iron in the body. Serum ferritin concentration has been used as a proxy of body iron stores. A definitive ratio between cord serum ferritin and neonatal iron stores has not been established. The ratio is estimated to be lower in newborn infants (1 μg/L of serum ferritin being equivalent to 2.7 mg of stored iron) than in adults (1 μg/L serum ferritin being equivalent to 8–10 mg stored iron).[56] The gestational-age-specific cord serum ferritin concentrations range from a mean concentration of 63 μg/L at 23 weeks to a mean value of 171 μg/L at 41 weeks.[57] In pre-term and full-term infants, the 5th percentile cord serum ferritin concentrations are 35 μg/L and 40 μg/L, respectively. As with other age groups, low serum ferritin concentrations are seen only in conditions of iron deficiency in the perinatal period. However, serum ferritin is increased in inflammatory conditions, following erythrocyte transfusions and in neonatal hemochromatosis.

Serum iron and transferrin saturation are other measures utilized in the assessment of iron status, although neither measure is sensitive for this purpose during the perinatal period. The utility of newer biomarkers, such as prohepcidin and hepcidin in cord blood or urine has not been adequately studied in the perinatal period.[49]

In summary, there are no stand-alone biomarkers for the measurement of iron status in all compartments during the perinatal period. Combination of multiple markers is likely to provide better information on the body iron status. Serum ferritin measurement soon after birth may help to identify those at risk for perinatal iron deficiency and its consequences.

Screening for iron deficiency beyond the perinatal period

The American Academy of Pediatrics (AAP) recommends screening full-term infants for iron deficiency between 9 and 12 months of age, with a second screen 6 months later, i.e. at 15–18 months.[58] Full-term infants at risk for iron deficiency are preferably screened earlier (e.g. at

6 months). Routine screening beyond 24 months is currently not recommended, except in children who are at risk of iron deficiency due to dietary and environmental factors.

The optimal screening test for iron deficiency beyond the perinatal period has yet to be determined. Current recommendation is to screen for anemia using age-, gender- and population-specific Hb or hematocrit, with a confirmatory second laboratory measurement if the values are <5th percentile.[58] Increased erythrocyte protoporphyrin (>35 µg/dL whole blood or >3 µg/g Hb) can also be used as a screening test. An improvement in Hb (>10 g/L) or hematocrit (>3%) after 1 month of enteral iron supplementation (3–6 µg/kg per day) is then used for establishing iron deficiency as the cause of anemia. If there is no response to iron supplementation, other tests, such as microcytosis (RBC volume <70 fL), low RBC count (<4.0 $\times 10^{12}$/L), widened RDW (>17%) and lower serum ferritin concentration (<15 µg/L) are used to further differentiate iron deficiency from anemia due to other causes.[58]

Preterm infants are likely to benefit from early screening for iron deficiency after discharge from the hospital. Even though there are no special recommendations for preterm infants from the AAP, it is considered prudent to screen the iron status of these infants at 4 months of age. [58] Unfortunately, many preterm infants develop iron deficiency before this age,[59] depending on the number of RBC transfusions, the growth velocity and iron supplementation. A low serum ferritin concentration (<50 µg/L) at 2 months portends the risk of subsequent iron deficiency in preterm infants with birth weight of <1700 g.[60] Therefore, assessment of Hb and serum ferritin at 2 months, and thereafter every 2 months until 6 months of age, might be advantageous in preterm infants. Measurement of ZnPP:H may be useful for detecting iron-deficient erythropoiesis at and after discharge in preterm infants.[52]

Beyond 6 months of age, serum ferritin does not correlate well with measures of erythropoiesis in preterm infants.[52] Additional tests of iron deficiency, such as Hb, mean corpuscular volume, red cell distribution width, ZnPP:H ratio and transferrin saturation are necessary. Finally, the establishment of reticulocytosis following iron supplementation can also be considered diagnostic of preexisting iron deficiency in this population.

Prevention and treatment of perinatal iron deficiency conditions

Recommendations for iron nutrition for pregnant women and full-term and preterm infants are available.[1,58] The recommended dietary allowance for pregnant women is 27 mg/day of iron. [1] A recent study found that daily iron supplementation in a dose of 40 mg/day starting at 18 weeks of gestation prevents iron deficiency during pregnancy and postpartum in >90% of women in developed countries.[61] Doses as high as 100 mg/day might be necessary in areas with a high prevalence of iron deficiency.[62]

Full-term newborn infants with no risks for neonatal iron deficiency will maintain adequate iron status during the initial 4–6 months of life on breast milk that contains <1 mg of iron/L or on infant formula that contains 4–12 mg/L. The current AAP recommendation is to begin iron supplementation in all breastfed full-term infants at 4–6 months through iron-containing complementary foods. If iron cannot be provided through dietary sources, elemental iron at 1 mg/kg/day should be used after 6 months.[58] However, commencing iron supplementation at 1 month of age results in higher Hb, a decrease in the incidence of iron deficiency at 6 months of life, and an improvement in neurodevelopmental indices at 13 months of age in breastfed infants.[63] Thus, early supplementation can be beneficial in a select group of breastfed infants. Preterm infants require more iron than full-term infants as discussed below.

Absorption and retention of enterally administered iron depends on a variety of factors. Absorption is increased in iron-deficiency states and with increasing gestational and postnatal ages, and is decreased with larger doses and after a recent RBC transfusion.[64] The dietary

source also has a significant effect. The iron content of breast milk varies between 0.2 and 0.8 mg/L. Between 20 and 50% of breast milk iron is absorbed and retained by the infant.[65] The retention of iron from formula milk is much lower, ranging from 4 to 20%.

Between 7 and 54% of iron administered between feedings is retained by the infant[65]; 30–40% is probably a true representative value. Retention is better in infants who are fed breast milk than in formula-fed infants, in those with iron deficiency and if supplementation is begun after postnatal erythropoiesis has commenced. The percentage retained varies inversely with the dosage administered, except in ELBW infants <1 month of age.[22,65] Unlike adults, only a portion (12–55%) of absorbed iron is promptly incorporated into erythrocytes in infants.[65]

Unless there is a need for long-term parenteral nutrition (e.g. total bowel resection), parenteral iron administration is rarely used in infants. The dose in such situations is 100–200 μg/day. [66] RBC transfusion is another method of delivering iron parenterally, but exposes the infant to transfusion-related complications.

Maternal iron deficiency—Most gestational iron supplementation studies have focused on the beneficial effect of such supplementation in reducing the risk of preterm birth and low birth weight.[3] Treatment of the iron-deficient mother with additional dietary iron results in increased iron transport to the fetus, even at the expense of maternal iron status.[67] The serum ferritin concentration is increased at birth and at 3 months in infants of iron-deficient mothers who received iron supplementation during gestation.[6,62] An additional benefit of maternal iron supplementation is prevention of preterm birth, which allows additional time for the fetus to accrete iron. To be effective, iron supplementation should be started earlier, preferably pre-pregnancy.[3] Oral supplementation is more effective than parenteral supplementation[67] and is also safer.

Another method of enhancing neonatal iron status is delayed clamping of the umbilical cord at birth. The infant can receive a transfusion of 20–30 mL/kg of blood, depending on the time of clamping and the position of the infant in relation to the mother. This translates to approximately 15–25 mg/kg of additional iron endowment. A 30–120-s delay in clamping of the cord improves the iron status during the initial 2–3 months of life in full-term and preterm infants.[68] This practice is particularly beneficial for infants born to mothers with iron deficiency, those with birth weight <3000 g and those not given iron-fortified formula.[69] The role of delayed umbilical cord clamping in ELBW infants, IUGR infants and in populations with adequate maternal iron endowment has not been studied.

Infants with iron deficiency have altered temperament and cognition and are at risk for earlier onset of postnatal iron deficiency. Breastfed infants who are supplemented with iron in a dose of 7.5 mg/day from 1 month of age perform better in neurodevelopmental tests at 1 year of age.[63] Additional studies are necessary to determine the role of such supplementation.

Maternal diabetes mellitus—The abnormalities in iron metabolism in IDM are a function of maternal glycemic control. Maternal iron supplementation is unlikely to improve fetal iron status, as the majority of mothers with diabetes mellitus are iron sufficient. Adequate maternal transferrin saturation will impede absorption of supplemented iron from her gastrointestinal tract. Furthermore, placental iron transport will also be partially dependent on the degree of saturation of maternal transferrin. It is possible that iron supplementation after birth might more rapidly replete the depleted iron stores in iron-deficient IDM. However, the efficacy of such therapy in normalizing the iron status and in correcting neurobehavioral impairments has not been studied. Therefore, routine iron supplementation beyond what is available from human milk and infant formula is not recommended.

IUGR due to maternal hypertension—IUGR due to maternal malnutrition can benefit from iron supplementation during gestation, as malnourished women are also likely to be iron deficient. Iron supplementation of hypertensive mothers with IUGR fetuses is not likely to be successful for reasons similar to cases of IDM discussed above. However, screening for and treatment of maternal hypertension could potentially reduce placental vascular disease and normalize iron transport. Furthermore, adequate oxygenation of the fetus through improved placental blood flow will reduce fetal iron needs for augmented erythropoiesis.

Overall, newborn infants with IUGR have low total body iron and are at risk of earlier postnatal iron deficiency. Thus, earlier screening (at 6 months instead of 9 months) for iron deficiency is prudent. Currently, there are no special recommendations to increase iron delivery to full-term IUGR infants beyond what is considered adequate in appropriate-for-gestation infants. However, it might be prudent to dose these infants in a manner similar to premature infants of similar birth weights (2–4 mg/kg per day).

Maternal smoking—Cessation of smoking is the most effective way to prevent iron abnormalities in the fetus and neonate. No recommendations exist for additional iron supplementation of appropriate-for-gestation newborn infants whose mothers smoked during pregnancy. However, heavy smoking can result in IUGR, presumably with attendant reductions in total body iron. Moreover, infants born to mothers who smoked during gestation are at risk of iron deficiency until 24 months of age.[38] Therefore, it might be advisable to subject the infants of mothers who smoked during gestation to early screening for iron deficiency and to supplement them with additional iron.

Preterm infants—Preterm infants exhibit a wide range of iron status at discharge, depending on their degree of prematurity, amount of phlebotomy losses, number of red cell transfusions, bouts of infection, and timing and dosing of iron supplementation. Limiting phlebotomy losses and starting iron therapy at 2 weeks (as opposed to 2 months) of postnatal age might be effective preventative strategies against subsequent iron deficiency.[70] The AAP recommends that preterm infants receive 2–4 mg of enteral iron/kg per day.[58] Infants receiving rHuEpo therapy should receive at least 6 mg/kg per day. Intravenous iron, although extremely effective in supporting erythropoiesis, might confer an increase of oxidative stress.[71]

It is not possible to provide dosing recommendations for preterm infants with altered iron distribution characterized by anemia and high serum ferritin concentrations because their total body iron status is unknown. It remains unclear whether and when iron sequestered in their livers will be released for utilization by the bone marrow. Furthermore, it appears that enterally dosed iron might be sequestered in the liver before becoming available for erythropoiesis,[71] potentially further exacerbating their hyperferremia without improving erythropoiesis.

After discharge, premature infants continue to have increased iron needs because of the rapid growth rate during the first postnatal year. There is a high rate of iron deficiency in preterm infants fed low-iron formulas or breast milk.[72] Current preterm discharge formulas provide approximately 1.8–2.2 mg of iron/kg per day, assuming a typical consumption of 150–160 mL/kg per day. Recent data suggest that preterm infants with low serum ferritin concentrations might require additional iron supplementation.[57] It might be prudent to supplement formula-fed pre-term infants with iron in a dose of 1 mg/kg per day.[58]

Management of iron-overload conditions during the perinatal period

Neonatal hemochromatosis

There is an 80% probability that this condition will recur in subsequent pregnancies.[39] As an alloimmune mechanism is thought to be involved in the pathogenesis of the condition,

intravenous immunoglobulin administration during subsequent pregnancies might improve perinatal outcome.[39,73]

Newborn infants with hemochromatosis are extremely ill and require intensive care. Relatively asymptomatic newborn infants with hyperferremia have been described and might represent heterozygotes of the more severe form of hemochromatosis. Iron chelation combined with a cocktail of antioxidants started soon after birth and continued until serum ferritin levels are <500 mg/L is successful in some patients.[41] Liver transplant might be necessary but is often not feasible because of the smaller size of these infants; the results are not encouraging.[41] It seems prudent to place infants with hemochromatosis or hyperferremia on low-iron diets once they recover.

Other perinatal conditions associated with iron overload

Infants undergoing cardiopulmonary bypass might benefit from iron chelation.[47] Infants with potential iron-induced damage from reperfusion following hypoxic–ischemic injury have not been studied with respect to iron dosing. For the most part, the reperfusion injury occurs when they are ill and are not receiving enteral or parenteral iron. Animal models demonstrate that administration of the iron chelator, desferoxamine, before the ischemic event reduces neurologic morbidity.[74] It is unclear whether post-event chelation would be effective in reducing the amount of damage. Similarly, it is not known whether delaying iron supplementation improves neurologic outcome. Finally, iron supplementation might be delayed in preterm infants who have increased serum ferritin concentrations due to multiple RBC transfusions.

Conclusions and future directions

Most of the perinatal iron deficiency conditions can be prevented through optimal management of gestational conditions in their mothers. Ensuring maternal iron sufficiency during gestation is probably the most cost-effective method of preventing perinatal iron deficiency. However, iron excess during gestation also appears to increase the risk of perinatal complications in the fetus and the mother. Additional studies are necessary to determine the role of routine iron supplement in iron-adequate mothers. Additional research is also necessary to assess the effects of iron deficiency on tissue iron status and organ function in various perinatal iron deficiency conditions. To be meaningful, these studies should be long term and should include remedial measures in a randomized controlled fashion. Comprehensive laboratory methods that are sensitive and specific for diagnosing abnormal iron homeostasis and their long-term effects have to be developed. Finally, research is necessary to develop nutritional and non-nutritional interventions that complement iron supplementation and prevent or reverse the long-term adverse sequelae of perinatal iron deficiency.

> **Practice points**
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> - Both iron deficiency and iron excess during the perinatal period are detrimental.
>
> - Reduced iron delivery from the mother and/or increased fetal iron demand beyond the placental transport capacity result in perinatal iron deficiency.
>
> - A serum ferritin concentration <35 μg/L at birth indicates significant depletion of storage and tissue iron.
>
> - Long-term neurodevelopmental impairments and predilection for early postnatal iron deficiency are the principal sequelae of perinatal iron deficiency.
>
> - Maternal intervention is the best way to prevent iron deficiency in the newborn infant.

- Infants with perinatal iron deficiency should be screened for iron deficiency early during infancy.

- Exclusive breastfeeding and avoidance of cow's milk and low-iron formula are effective in preventing postnatal iron deficiency in full-term infants.

- Limiting phlebotomy losses and early iron supplementation are effective in preventing iron deficiency in preterm infants.

- Due to the potential for oxidative stress, indiscriminate iron supplementation should be avoided in preterm infants.

Research directions

- The role of routine iron supplementation in mothers with adequate iron stores.

- Assessment of tissue iron status in maternal iron deficiency, maternal smoking and preterm infants and their relationship to long-term sequelae.

- Development of biomarkers for diagnosing iron status in different compartments and for predicting neurodevelopmental outcome.

- Development of complementary nutritional and non-nutritional strategies to counter the adverse effects of perinatal iron deficiency.

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