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Iron Therapy for Preterm Infants

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SYNOPSIS

Preterm infants are at risk for both iron deficiency and iron overload. The role of iron in multiple organ functions suggests that iron supplementation is essential for the preterm infant. Conversely, the potential for iron overload and the poorly developed anti-oxidant measures in the preterm infant argues against indiscriminate iron supplementation in this population. The purpose of this article is to review the predisposing factors and consequences of iron deficiency and iron overload in the preterm infant, the current recommendation for iron supplementation and its appropriateness, and describe potential management strategies that strike a balance between iron deficiency and iron toxicity.

Keywords

guidelines; infant; iron; iron overload; premature; therapy

INTRODUCTION

The need for iron therapy in preterm infants has been debated at least since the 1950s [1]. The essential role for iron in various tissue functions and their propensity to develop iron deficiency suggest that iron supplementation is essential to the preterm infants. Conversely, the pro-oxidant role of non-protein bound iron and the poorly developed antioxidant measures in preterm infants cautions against aggressive iron supplementation in this population. It is not surprising that there are wide variations in iron supplementation practices among neonatal units [2].

RISK OF IRON DEFICIENCY IN PRETERM INFANTS

Between 25% and 85% of preterm infants develop evidence of iron deficiency during infancy [3–8]. Unlike full term infants, in whom the condition typically occurs during the second half of infancy, preterm infants are at risk for developing iron deficiency during their first 6 postnatal

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months [5–9]. Gestationally more premature and smaller preterm infants are at greatest risk for developing iron deficiency at an earlier age [5,9,10]. Iron deficiency is more common in preterm infants from developing countries [4] and in those consuming human milk exclusively without supplementation.

Factors predisposing to iron deficiency

A number of factors combine to predispose the premature infant to negative iron balance. Iron is mostly accumulated during the third trimester of gestation [11]. Total body iron and hemoglobin (Hgb) contents, and serum and storage iron concentrations are lower in preterm infants [11–13]. Conditions such as severe maternal iron deficiency [14], intrauterine growth restriction [12,15,16], and chronic blood loss during gestation can further compromise fetal iron endowment.

Postnatally, the meager iron stores can be rapidly depleted during the first 6–8 weeks, coinciding with the onset of erythropoiesis and rapid catch-up growth [1,5,15]. The Hgb nadir is lower and occurs earlier in more premature (gestational age 28–32 wk) infants when compared with those born at a gestational age of 33–36 wk [3]. However, beginning at 9 weeks and continuing until 12 months of age, Hgb concentrations are comparable in the two gestational age groups [3], implying the need for a more robust erythropoiesis and therefore, greater iron requirement in the more prematurely born infants.

Tissue iron stores are depleted sooner in those preterm infants demonstrating the greatest growth velocity [15]. This is seen particularly with more immature preterm infants who demonstrate the most rapid catch-up growth [1]. Interestingly, the iron status at birth does not influence postnatal growth rate [17], signifying that preterm infants will grow whether they are iron replete or not at birth. The high rate of postnatal catch-up growth with its attendant increases in blood volume and Hgb mass requires additional iron. Unless augmented by external sources, the endogenous iron stores of preterm infants at birth meet their iron demands only until the doubling of the birth weight, i.e., approximately until 2–3 months of age [18]. Chronic gastrointestinal hemorrhage and clinical practices, such as uncompensated phlebotomy losses and inadequate iron supplementation further deplete iron stores and increase iron requirements.

Consequences of iron deficiency

The effects of iron deficiency are pervasive and involve multiple organ systems. Poor physical growth, gastrointestinal disturbances, thyroid dysfunction, altered immunity and temperature instability has been attributed to iron deficiency in very low birth weight (VLBW, birth weight <1500 g) infants [19]. Anemia is typically a late sign and suggests significant depletion of iron stores. A major concern of early iron deficiency is its effect on the developing brain.

Potential effects of iron deficiency on neurodevelopment—Dietary iron deficiency during early infancy is associated with long-term neurodevelopmental impairments that appear to be irreversible in spite of iron supplementation (Reviewed in [20]). Long-term cognitive abnormalities have also been demonstrated in full-term infants with iron deficiency in the neonatal period [13,21].

A limited number of studies suggest that early iron deficiency may also adversely affect neurologic function and neurodevelopment in preterm infants. Compared with non-anemic, iron-replete infants, preterm infants with anemia (Hgb ≤10 g/dL) and low iron stores (serum ferritin ≤ 76 μg/L) had an increased number of abnormal neurologic reflexes at 37 wk postmenstrual age [22]. A recent study demonstrated more mild neurologic abnormalities, such as broad gait, dysdiadochokinesis or dysmetria at 5 years of age in preterm infants who received

iron supplementation from 2 months of age, compared with those supplemented from 2 weeks after birth [23]. A trend toward poorer cognitive performance was also present in those supplemented late [23]. Thus, early iron deficiency appears to adversely affect neurodevelopment in preterm infants. Interestingly, unlike the cognitive deficits that tend to predominate in full-term infants with neonatal iron deficiency [13,21], motor deficits appear to predominate in preterm infants.

RISK OF IRON OVERLOAD IN PRETERM INFANTS

In the absence of genetic conditions, such as congenital hemochromatosis, iatrogenic factors are responsible for excessive iron accumulation in preterm infants. However, there are no specific data on the incidence of iron overload due to nutritional iron therapy in preterm infants.

Factors predisposing to iron overload

Multiple erythrocyte transfusions may lead to excess iron accumulation in preterm infants. Approximately 80% of VLBW and 95% of extremely low birth weight (ELBW, birth weight <1000 g) infants receive erythrocyte transfusions during their hospitalization [24]. Compared with adults, the mean life span of transfused erythrocytes is shorter in preterm infants [25]. The accelerated breakdown of erythrocytes may lead to excess iron accumulation [26] and a need for repeated transfusions. Each mL of transfused packed erythrocytes potentially delivers 0.5–1.0 mg of iron to the body [27,28]. Elevated serum iron and ferritin concentrations, and liver iron concentration are common after multiple transfusions in preterm infants [29–31]. Preterm infants who have received multiple transfusions may maintain iron stores without iron supplementation up to 6 months of life [30,32,33].

Although the serum iron concentration transiently increases after intravenous administration of iron in preterm infants [34], there are no data that this practice leads to iron overload at commonly used dosages. Similarly, there is no evidence for excess iron accumulation with enteral iron administration at doses typically used for supplementation [35,36].

Consequences of iron excess in preterm infants

As with iron deficiency, excess iron accumulation potentially affects multiple organ systems. Large doses of enteral iron administration were associated with hemolysis in preterm infants with vitamin E deficiency [37]. This nutritional deficiency is rare at present. There is an association between multiple erythrocyte transfusions and retinopathy of prematurity (ROP) [29,38] and bronchopulmonary dysplasia (BPD) [30,39]. The incidence and severity of both conditions correlate with the number and volume of erythrocyte transfusions [29,30]. While it is tempting to speculate that transfusion-related iron overload may be involved in the pathogenesis of these conditions, other studies have failed to provide such evidence [40].

Non-protein bound (“free”) iron mediated oxidative stress in the presence of poor antioxidant capabilities has been postulated to initiate or potentiate the progression of BPD and ROP through generation of reactive oxygen species (ROS) [30,39]. Multiple studies have demonstrated that the milieu in preterm infants is conducive for iron to exist in the pro-oxidant ferrous state and for the formation of ROS [3,26,39]. Additionally, although ferritin iron is protein-bound, there is potential for release of free iron from ferritin during oxidative stress [41].

Nevertheless, assigning a direct causative role for iron in BPD and ROP has been problematic. Infants developing these multi-factorial conditions tend to be more premature and sicker and thus, more likely to receive multiple transfusions. It has yet to be established *in vivo* that iron is directly involved with oxidative stress in preterm infants [27,30,38,42]. Increased serum iron concentration following multiple transfusions was not associated with lipid peroxidation in

preterm infants with BPD [30], nor was increased hepatic iron concentration in multiply transfused preterm infants associated with hepatocyte injury [31]. Unfortunately, most of the assessments have been short-term and assessed oxidative stress soon after a single transfusion [27] or short duration of enteral iron administration [42,43]. Long-term studies are necessary to conclusively assess the risk of oxidative stress and tissue injury with cumulative doses of iron administration in preterm infants.

Potential effects of iron overload on neurodevelopment—Iron overload is postulated in the pathogenesis of ischemic brain injury and many neurodegenerative disorders in adults [44]. Similarly, increased non-protein bound iron and lipid peroxidation products have been demonstrated in the CSF of newborn infants with birth asphyxia [45]. These are non-nutritional effects of iron. Parkinson-like neurodegeneration in adulthood has been demonstrated in mice following enteral administration of large doses of iron (approximately 40 times that present in own mother's milk) during the lactation period [46]. While this animal study is concerning, long-term neurodevelopmental deficits due to iron supplementation at typical doses have yet to be demonstrated in human infants.

In summary, the preterm infant is at risk of both iron deficiency and iron overload. Due the potential adverse impact of iron deficiency on developing organ systems, preventive and therapeutic measures appear to be crucial. Conversely, the potential for organ injury with excess iron suggests that iron therapy should be instituted carefully in the preterm infants.

PREVENTIVE MEASURES FOR IRON DEFICIENCY

Determining the iron requirements of preterm infants

The goal of nutrient delivery to preterm infants is to mimic the intrauterine accretion rate and maintain normal serum levels [47]. Using this analogy, a preterm infant would require a daily iron intake of 1.6–2.0 mg/kg intravenously [48] or 5–6 mg/kg enterally, since enteral iron absorption is approximately 30% [49]. However, such supplementation is neither practical nor physiological soon after birth. Enteral nutrition is not feasible soon after birth in most VLBW preterm infants. Unlike intrauterine life, growth and erythropoiesis cease soon after birth. Iron requirements are lower under those circumstances. Estimates of daily requirements based on a factorial approach [50] are also likely to be imprecise [51]. Well-executed, randomized controlled trials are probably the best method to determine the iron requirements of preterm infants. These trials have established the beneficial effect of iron supplementation via fortification of human milk, iron-fortified formula and medicinal iron in decreasing the risk of iron deficiency [8,16,51–53]. However, most studies have evaluated only short-term benefits on hematological parameters. There is a paucity of information on the long-term effects of iron supplementation on hematological and non-hematological parameters, such as growth and neurodevelopment.

ENTERAL IRON SUPPLEMENTATION THROUGH DIET

Fortification of human milk

The iron content of human milk is approximately 0.5 mg/L [54]. Whereas human milk meets the iron requirements of full-term infants during the first 4–6 months of age, additional iron is necessary to meet the needs of erythropoiesis and growth of preterm infants [16]. The iron status of preterm infants receiving non-fortified breast milk starts to deteriorate within 1 to 4 months [7,9,10]. Cow milk-based human milk fortifiers that are currently available in the United States contain 3.5–14.4 mg/L of iron and deliver 0.7–2.2 mg/kg d^{-1} of additional iron if milk consumption is 150 mL/kg d^{-1}. Fortification with an iron-fortified human milk fortifier is associated with fewer erythrocyte transfusions than fortification with a low-iron fortifier [52]. Therefore, additional iron supplementation may be necessary if the latter is used. The

currently available human milk-based human milk fortifier in the United States is also not fortified with iron and provides only 0.3 mg/kg d^{-1} of iron if daily milk consumption is 150 mL/kg.

Use of iron-fortified formula

Compared with a formula lacking iron, weaning to an iron-fortified formula improves Hgb and serum ferritin concentrations in preterm infants [16]. Preterm infants with birth weights <1800 g will not achieve iron sufficiency on a formula containing ≤3 mg/L [6]. Formulas containing 5–9 mg/L of iron appear to meet the iron requirements of erythropoiesis in healthy preterm infants during the first 6 months of life [55]. However, 18% of the infants receiving the 9 mg/L formula and 30% of those receiving the 5 mg/L formula developed iron deficiency (serum ferritin concentration <10 μg/L) between 4 and 8 months of age in that study [55]. The currently available infant formulas in the United States are fortified with 12.0–14.4 mg/L of iron and deliver 1.8–2.2 mg/kg d^{-1} when consumed at 150 ml/kg d^{-1}. The discharge formulas have an iron content of 13 mg/L and provide approximately 2 mg/kg d^{-1} of iron.

ENTERAL SUPPLEMENTATION THROUGH MEDICINAL IRON

Enteral administration is commonly used for supplementing iron to preterm infants. There are wide variations in the dose, initiation and duration of supplementation and iron compounds used for enteral supplementation [2]. The recommendations of various pediatric societies [47,56,57] are given in table 1. Iron supplementation is not recommended nor is it necessary during the transition period soon after birth [56]. An exogenous source of 2–4 mg/kg d^{-1} iron is recommended during the period of stable growth, beginning at 4–8 weeks and continuing until 12–15 months of age (Table 1). Whereas these recommendations provide useful guidelines for iron therapy in preterm infants, they may not be universally applicable as discussed below.

Dosage of elemental iron

At least 2–4 mg/kg d^{-1} of elemental iron is necessary to prevent iron deficiency in non-transfused VLBW infants [5,58]. However, their Hgb level does not reach that of full term infants by 9 months of age with such supplementation [58]. Even with 4–6 mg/kg d^{-1} of iron supplementation from 2 wk of age, iron deficiency is found at 2 months of age in approximately 15% of preterm infants with birth weight <1301 gm [8]. Preterm infants with lower birth weight and gestational age demonstrate more robust erythropoiesis and greater growth velocity than heavier and more mature counterparts [3]. At the same time their iron endowment at birth is lower. A scaled dosage based on gestational age and/or birth weight may be more appropriate [56,59]. Conversely, approximately 95% of ELBW infants receive erythrocyte transfusions [24] and are likely to have larger iron stores. Therefore, body iron stores should also be taken into consideration while deciding additional iron supplementation in ELBW infants. Preterm infants who are small-for-gestational age also may benefit from a higher dose of iron, as they potentially have lower total body iron concentration than appropriate-for-gestation counterparts [16].

Initiation of supplementation

The initiation of iron supplementation in preterm infants has been debated since the 1950s [1] and has ranged from 14 days to 10 weeks among the neonatal units [2]. The current recommendation is to begin supplementation from 4–8 wks of age, irrespective of gestational age or birth weight (Table 1).

However, beginning supplementation earlier may be prudent for the more immature preterm infants, many of who may be in negative iron balance by one month of age [9,33]. Compared

with unsupplemented infants or who were supplemented from 4–8 wk of age, supplementing 2–5 mg/kg d^{-1} of iron from 2 weeks of age reduces the need for erythrocyte transfusions and the risk of iron deficiency between 2 and 6 months of age [5,8,53]. Cumulative iron intake with early supplementation was calculated to be > 3 times of late supplementation [8]. Hgb, serum iron and ferritin concentrations were higher and serum transferrin (Tf) receptor concentrations lower at 2 months of age with early iron supplementation [8,53], suggesting better iron stores at discharge. Early iron supplementation was tolerated well and was not associated with morbidities. A follow-up study demonstrated a lower incidence of mild motor signs and a trend towards better cognitive function at 5 years of age in those supplemented from 2 weeks [23], suggesting potential long-term benefits with early supplementation. The lack of long-term neurological morbidity also supports the safety of early iron supplementation.

On the other hand, the risk of iron-induced hemolysis in preterm infants with vitamin E deficiency is maximal during the first 6 weeks of life [37]. Serum iron and ferritin concentrations remain elevated during the first 4–6 wk of life even without supplementation. [3]. There is a potential for iron excess with higher doses of supplementation since enteral iron absorption appears to be poorly regulated during the first month of life in ELBW infants [9, 10,51]. Furthermore, supplemental iron is better incorporated into red cells when it is administered after the onset of erythropoiesis [60]. These studies would support delaying iron supplementation until 4–6 wk.

Duration of supplementation

The duration of supplementation has varied from 6 to 12 months [2]. Most organizations recommend supplementation until 12–15 months of age (Table 1). The optimal duration of supplementation has yet to established in randomized controlled trials.

Choice of iron compound for supplementation

Ferrous sulfate is commonly used for supplementation, as well as for fortifying formula. It is inexpensive and widely available. Even though there are theoretical advantages for using non-ionic ferric compounds, studies have not established their superiority over ferrous sulfate vis-à-vis tolerance, efficacy and complications [61]. Moreover, whereas ferrous sulfate may be administered once daily [62], some of the other compounds require more frequent administration [61], which may compromise compliance.

Route of supplementation

Parenteral iron administration is not typically used for routine iron supplementation. As iron is not naturally excreted in stools or urine, almost all of the parenterally administered iron would be retained in the body. Intramuscular administration of iron is as efficacious as oral supplementation in ameliorating iron deficiency [63]. Nevertheless, the practice is discouraged because of associated pain and complications [64]. Intravenous iron administration is safe and more effective than enteral iron for supporting erythropoiesis [28,34,35]. Even though iron is accreted at a rate of 1.6–2.0 mg/kg d^{-1} during the third trimester [48], an intravenous dose of 120 μg/kg d^{-1} results in a positive iron balance [28], likely due to decreased iron requirements soon after birth. Between 18% and 68% of the intravenously administered iron is incorporated into erythrocytes within 2 weeks [60,65]. Intravenous administration is also thought to improve growth in preterm infants receiving rHuEPO [66]. Nevertheless, the transient elevation of malondialdehyde, a marker of lipid peroxidation, at the conclusion of iron infusions [34], cautions against routine supplementation through this route. The need for long-term intravenous access also makes it impractical for most infants.

Iron supplementation in special circumstances

Iron supplementation during recombinant human erythropoietin (rHuEPO) therapy—Administration of rHuEPO promotes erythropoiesis and reduces the need for erythrocyte transfusions in preterm infants (see [67] for a review). Iron supplementation is necessary since rHuEPO administration depletes body iron stores [35,68]. A daily intake of 3–8 mg/kg of iron appears to be adequate for supporting erythropoiesis, is well-tolerated and does not appear to be associated with oxidative stress [35,66,67,69]. The Committee on Nutrition of the American Academy of Pediatrics recommends enteral supplementation of 6 mg/kg d^{-1} of elemental iron during rHuEPO administration [47]. However, this dose may not be sufficient to support erythropoiesis and maintain iron stores [70]. Simultaneous enteral (9 mg/kg d^{-1}) and parenteral (2 mg/kg d^{-1}) iron administration [34] or continuation of enteral iron therapy beyond rHuEPO administration [66] may be necessary to achieve this goal. Enteral doses as high as 18–36 mg/d (approximately 12–24 mg/kg d^{-1}) have been used [71], but do not appear to provide additional benefits and may cause hematochezia [66].

Intravenous iron supplementation in a dose of 2–6 mg/kg or 20 mg/kg weekly may improve erythropoietic response and growth during rHuEPO therapy [70]. Such therapy may be useful in infants with low serum ferritin levels or in whom enteral nutrition has yet to be established. Intramuscular administration of 1 mg/kg d^{-1} or 12 mg/kg once weekly during rHuEPO therapy also appears to be effective [67,72]. Overall, a prudent approach may be to adjust the iron dose to maintain serum ferritin concentration >100 μg/L during rHuEPO therapy [73].

Iron supplementation in preterm infants with elevated serum ferritin concentrations—It is not unusual for preterm infants to have abnormally high serum ferritin concentrations (>350 μg/L). This may occur due to storage of excess iron following multiple transfusions (i.e., true iron overload) or sequestration of iron during periods of inflammation (i.e., iron redistribution). There are no specific guidelines with respect to iron supplementation of preterm infants with high serum ferritin concentrations. The increased risk of mortality and morbidity associated with iron supplementation in iron-replete infants and children [74] and the potential for additional iron accumulation due to the poor regulation of intestinal absorption [9,51,74] cautions against routine supplementation in these infants. Nevertheless, some of the preterm infants with elevated serum ferritin may simultaneously have iron-deficient erythropoiesis [51], suggesting an inability to release ferritin bound hepatic iron to the bone marrow. Therefore, it may be prudent to rule out iron-deficient erythropoiesis by determining the zinc protoporphyrin to heme (ZnPP/H) ratio and reticulocyte count [75] in infants with increased serum ferritin levels and consider iron supplementation on an individual basis. Preterm infants in whom iron supplementation has been withheld will likely benefit from periodic screening of their iron status as they may be at risk of iron deficiency during the post-discharge period. A recent study of small sample size demonstrated evidence of iron deficiency between 6 and 12 months corrected age in approximately 25% of preterm infants who had serum ferritin concentration >95th percentile of normal at discharge, in spite of receiving 2–4 mg/kg d^{-1} of iron [76].

Post-ingestion considerations

Absorption and retention—The absorption of iron from human milk is >50% and from cow milk based formulas is approximately 4–12% [77]. Absorption is better from whey-predominant formula than casein-based formula. Only 1–7% of iron in soy milk-based formula is absorbed [77].

The absorption and retention of enterally administered medicinal iron depends upon the postnatal age and iron status of the infant. Absorption is better if medicinal iron is supplemented with breast milk or between meals [49,60]. Isotope studies have demonstrated that

approximately 25–30% of the administered iron is absorbed [9,49], irrespective of the iron endowment [51]. Approximately 10–25% of the iron supplemented between feeding is incorporated into erythrocytes within 2 weeks [60,65].

Adjuvant therapies to enhance the efficacy of enteral iron supplementation— Ascorbic acid and other organic acids in the diet favor absorption. However, there are no specific recommendations for administering these or other nutrients during iron supplementation. Although rHuEPO promotes incorporation of absorbed iron into erythrocytes, it does not enhance enteral iron absorption [78].

Gastrointestinal tolerance—Iron-fortified infant formulas are well tolerated in full-term infants and may be used as the first feeding when breast milk is not available [77]. Gastrointestinal symptoms, such as cramping, gastroesophageal reflux and flatulence that are attributed to ingestion of iron have not been borne out by controlled studies of iron-fortified formulas [79]. Similarly, medicinal iron in doses of 2–10 mg/kg d^{-1} is well tolerated by preterm infants [5,8,42,53]. However, clinically significant hematochezia without necrotizing enterocolitis occurred in 17% of preterm infants receiving 8–16 mg/kg d^{-1} of elemental iron, necessitating cessation of supplementation [66]. Whether hematochezia was due to iron *per se* or to other factors (for example, allergy to cow milk protein) was not established. In most instances iron therapy could be resumed upon the resolution of hematochezia [66]. Other studies have reported tolerance of 18–36 mg/d of iron supplementation without gastrointestinal side effects [71].

Interaction of iron with other minerals—As many divalent cations share common transport mechanisms [80], there is a potential for interaction between iron and other minerals. The effect on zinc and copper has been studied in detail. Zinc supplementation does not appear to impede iron absorption at a ratio of 4:1 in formula [81]. Similarly, there was no effect of 2 mg/kg d^{-1} of iron supplementation on serum zinc levels [82] or selenium absorption [83]. Iron absorption from fortified breast milk appears to be intact in spite of the high calcium content of the fortifier [60]. Even though iron supplementation appears to alter copper metabolism, its clinical relevance is unclear at present [51].

Oxidative stress with enteral iron supplementation—*In vitro* studies have demonstrated increased free radical and lipid peroxidation products in formula and human milk after addition of medicinal iron [84]. There are no *in vivo* studies demonstrating oxidative injury following enteral iron supplementation. Preterm infants between 27 and 34 weeks gestation had no increase in iron overload and oxidative stress with a formula fortified with 8 mg/L of iron [85]. Enteral iron supplementation in doses of 3–10 mg/kg d^{-1} was not associated with markers of oxidative stress in plasma and urine of stable VLBW infants [42,43]. Nevertheless, a threshold dose of iron likely exists beyond which the potential for oxidative stress increases.

OTHER PREVENTIVE MEASURES FOR IRON DEFICIENCY

Delaying the clamping the umbilical cord 30–180 sec after birth improves iron status [86]. However, data are insufficient to recommended this practice as a general policy, given the potential impact of a large volume expansion on the fragile cerebral circulation of the preterm infant. Limiting phlebotomy losses, avoiding cow milk and using iron pots for cooking [4] are other preventive measures that may improve the iron status of preterm infants. Of note, it is not possible to enhance iron concentration of the breast milk with maternal iron supplementation after birth [54].

SCREENING AND TREATMENT OF IRON DEFICIENCY ANEMIA IN PRETERM INFANTS POST DISCHARGE

Timing and frequency of screening

Periodic assessment of Hgb or hematocrit is recommended for screening the iron nutritional status of full term infants, with an initial screening between 9 and 12 months of age and a second screening 6 months later (i.e., between 15 and 18 months) [87]. Although there are no specific recommendations for preterm infants, it is considered prudent to them at approximately 4 months [87]. As many preterm infants develop iron deficiency prior to that age [8,15], screening at 2 months or at discharge, whichever is earlier, appears prudent. In one study, serum ferritin <50 μg/L at 2 months predicted future risk of iron deficiency in preterm infants [5]. Determining ZnPP/H ratio at the time of discharge may be useful for diagnosing iron deficient erythropoiesis and need for additional iron [75]. A recheck of hematological status at 6 months of age, instead of the recommended 9 months, may also be beneficial. An individualized follow-up schedule based on the iron status at discharge, growth velocity, type of milk feeding and dose of iron supplementation would be ideal.

Biomarkers of iron nutritional status

Many laboratory tests are available to comprehensively assess the iron nutritional status (See [88] for a review). However, their usefulness for diagnosing iron adequacy or deficiency is limited in preterm infants, as gestational age-specific normal values have yet to be established for most biomarkers [88]. Furthermore, many laboratory markers are confounded by normal developmental changes [89,90], associated morbidities (e.g. inflammation) and therapies (e.g. rHuEPO administration and transfusions).

Diagnosis and treatment of iron deficiency

Hgb below the age-specific norm, serum ferritin <10–12 μg/L and transferrin saturation <10–17% have been considered suggestive of iron deficiency anemia in preterm infants during the first 2–6 months of age [5,8,53]. A relative increase of the absolute reticulocyte count by >50% one week after starting iron supplementation has also been considered suggestive of preexisting iron deficiency [8]. There are no universally accepted treatment protocols for iron deficiency in preterm infants. Oral administration of 3–6 mg/kg d^{-1} of elemental iron for 3 months is recommended in confirmed cases of iron deficiency anemia [87]. A scaled dosing of 3–12 mg/kg d^{-1}, adjusted according to the ZnPP/H ratio has been demonstrated to improve erythropoiesis without causing oxidative stress in preterm infants [43].

Potential risk of neuronal injury with rapid iron replenishment

Animal studies have demonstrated upregulation of iron receptors and transporters in the brain regions during fetal and neonatal iron deficiency [91]. Thus, there is a potential for increased cerebral uptake and neuronal injury with excess amounts of iron supplementation [46]. Therefore, rapid correction of iron deficiency using erythrocyte transfusions or large doses of iron should be avoided.

PREVENTIVE AND THERAPEUTIC MEASURES FOR IRON EXCESS

Setting guidelines for erythrocyte transfusions based on specific hematological parameters would potentially avoid iron excess. However, there are practical difficulties in adhering to the practice [40], as transfusions are often administered for non-hematological reasons. Use of rHuEPO in lieu of transfusions may be another strategy. Nevertheless, most studies have demonstrated only a modest decrease in the frequency of erythrocyte transfusions with rHuEPO

use [67]. Furthermore, a conservative transfusion practice or rHuEPO administration in lieu of transfusion may negatively affect the iron stores after discharge [32].

There are no specific recommendations for managing preterm infants with transfusion-related elevated serum ferritin concentrations. Periodic monitoring of the iron status may suffice, as the increased serum ferritin concentrations spontaneously normalizes within 2 months corrected age in most instances [76] due to a combination of cessation of erythrocyte transfusions, accelerating growth and regulation of enteral iron absorption [9]. A cocktail of antioxidants and iron chelators has been demonstrated to reduce hepatocyte injury and serum ferritin concentration in neonatal hemochromatosis [92]. However, such therapies have not been studied in transfusion-related hyperferritinemia and may not be necessary, since hepatocyte injury has not been demonstrated with the increased iron deposition in preterm infants [31]. Addition of lactoferrin to formula or human milk decreases the levels of iron-induced oxidative products *in vitro* [84]. This potential benefit has yet to be established *in vivo*. There is a theoretical benefit in administering rHuEPO, especially if there is co-existing iron-deficient erythropoiesis, as rHuEPO decreases serum ferritin concentrations without inducing lipid peroxidation or altering antioxidant enzyme activities in preterm infants [93].

SUMMARY AND FUTURE DIRECTIONS

Iron deficiency and iron excess are significant nutritional problems in the preterm infant. The potential risk of neurodevelopmental impairments due to iron deficiency warrants frequent screening and preventive measures via fortification of breast milk or use of iron-fortified formula. Iron supplementation also appears to be effective and safe. Nevertheless, there are unresolved issues concerning the practice. Iron overload remains a significant concern in multiply transfused sick preterm infants because of their poorly developed anti-oxidant mechanisms. The management of preterm infant with iron overload has not been well studied. Careful monitoring and support during the newborn and post-discharge periods is necessary due to the highly variable iron status of preterm infants. There is a need to develop gestational age-specific laboratory markers for comprehensively assessing iron nutritional status. Most studies on iron status and iron supplementation were conducted before the era of improved survival of smaller and gestationally more immature preterm infants. Well-controlled randomized trials are necessary to establish iron therapy guidelines for these infants. Research is also necessary to establish the mechanism of absorption and regulation of iron homeostasis during typical development.

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Table 1

Enteral Iron Intake Recommendations for Preterm Infants in Stable Clinical Condition

Nutritional Committee/Pediatric Society	Recommended Supplementation			Additional Considerations
	Population and dose (mg/kg d^{-1})	Initiation	Duration	
Committee on Nutrition, American Academy of Pediatrics [47]	Infants on human milk: 2.0 Infants on formula milk: 1.0 During rHuEPO use: up to 6.0	1 mo	12 mo	Only iron-fortified formulas should be used in formula-fed preterm infants
Nutrition Committee, Canadian Pediatric Society [56]	Birth weight ≥1000 g: 2.0–3.0 Birth weight <1000 g 3.0–4.0	6–8 wk	12 mo corrected age	A formula containing 12 mg/L of iron may be used to meet the iron requirements of infants with birth weight ≥1000 g. Additional oral iron supplementation is necessary for formula-fed infants with birth weight <1000 g
Committee on Nutrition of the Preterm Infant, European Society of Paediatric Gastroenterology and Nutrition [57]	Infants on human milk: 2.0–2.5 (maximum, 15 mg/d) Infants on formula milk: 2.0–2.5 (maximum, 15 mg/d) from all sources	No later than 8 wk	12–15 months	A formula containing 10–13 mg/L of iron is required to meet total iron requirement without supplementation. Delay oral iron supplementation until erythrocyte transfusions have ceased.

Abbreviation: *rHuEPO*, recombinant human erythropoietin