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Iron supplementation for infants in the NICU: What preparation, how much, and how long is optimal?

Sandra Juul [a,b], Kendell German [a,*]

[a] Department of Pediatrics, Division of Neonatology, USA
[b] Institute on Human Development and Disability, University of Washington, 1959 NE Pacific St., Box 356320, RR542 HSB, Seattle, WA, 98195-6320, USA

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ABSTRACT

Infants born preterm or with other perinatal risk factors are at added risk for both iron deficiency and overload. Insufficient iron supplementation in the perinatal period is associated with long-term neurodevelopmental effects. Based on this, iron supplements must be targeted to infants' individual iron needs to avoid the adverse effects of both iron deficiency and overload. Enteral iron supplements have been the gold standard in iron supplementation of neonates for many years. However, emerging parenteral formulations may provide an alternative for some infants, such as those who are unable to tolerate oral supplements or who are refractory to enteral supplementation. Optimal dosing and timing of supplementation is an area of ongoing research. In this review, we will summarize available enteral and parenteral iron formulations, review iron measurement parameters, and identify outstanding questions and ongoing research.

1. Introduction

Iron is an essential micronutrient that plays a critical role in human health. It is especially important during pregnancy and early development. One of the primary functions of iron is oxygen transport, as it is a core component of hemoglobin which allows it to bind oxygen. In addition to its crucial role in oxygen transport, iron is critical for brain development, as it is essential for energy production, synaptogenesis, dendritogenesis, neurotransmitter synthesis, neuronal function, and myelination [1]. Given its essential role, iron metabolism is closely regulated. Enteral iron is absorbed from the gut lumen via the DMT-1 transporter and exits enterocytes via the ferroportin receptor before being transported in the circulation bound to transferrin. Iron can be sequestered in cells such as macrophages and hepatocytes and released back into the circulation through the ferroportin transporter. Hepcidin is produced by the liver and promotes the internalization and degradation of ferroportin, leading to the sequestration of iron within storage cells and hepatocytes, thus decreasing circulating iron [2].

Iron is transported across the placenta to the fetus, and various maternal morbidities can impact fetal iron loading, including maternal anemia, obesity, diabetes, smoking, and treatment of hemolytic conditions such as Rh isoimmunization [3–6]. Iron is predominantly transferred to the fetus in the third trimester of pregnancy, so preterm birth is a major risk factor for iron deficiency in neonates [7]. Infants admitted to the neonatal intensive care unit (NICU) are at added risk for iron deficiency due to post-natal risk factors, including high phlebotomy rates, rapid somatic growth and periods of *nil per os* (NPO). Due to its essential role in brain function and development, iron status during the perinatal period is particularly important.

Acknowledging the importance of iron sufficiency in developing neonates, various regulatory agencies have recommended iron supplementation for preterm and term neonates. The American Academy of Pediatrics (AAP) and United States (US) Centers for Disease Control and Prevention (CDC) recommend a minimum of 2 mg/kg/day of iron supplements for preterm infants, with transient increases up to 6 mg/kg/day depending on iron levels. For term neonates, 1 mg/kg/day of iron supplement is recommended for exclusively breastfed babies or the use of iron fortified formula.[8, 9] The Canadian Paediatric Society and European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have similar recommendations [10,11]. Other publications have recommended following ferritin levels closely in high risk populations, and supplementing with up to 12–18 mg/kg/day of oral iron supplements to maintain iron sufficiency [12], though this practice has not yet been adopted into national and international guidelines.

The hesitancy to increase iron supplementation recommendations

* Corresponding author. University of Washington, 1959 NE Pacific St., Box 356320, RR542 HSB, Seattle, WA, 98195-6320, USA.
E-mail addresses: sjuul@uw.edu (S. Juul), germank@uw.edu (K. German).

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likely stems from a concern regarding the risks of excess iron supplementation. Iron is a potential pro-oxidant and neonates are known to have immature anti-oxidant mechanisms for the first few weeks after birth [13]. Additionally, enteral iron absorption is regulated by hepcidin, but it is not clear whether this mechanism is fully functional in preterm infants. Once in the body, there are only a few mechanisms in place to remove excess iron, with blood loss and sloughing of iron-loaded enterocytes being the primary mechanisms. Based on this, there are concerns regarding excess iron supplementation, particularly through avenues that bypass the hepcidin regulation axis, such as parenteral administration. Finally, iron supplementation has been associated with worse morbidity during certain infections, particularly gram-negative sepsis and malaria [14,15]. Therefore iron supplementation should be adjusted in these contexts.

In sum, iron is an essential micronutrient that plays key roles in oxygenation and brain development. Deficiency during key periods of development may have life-long implications [1]. Because of this, individuals, and particularly neonates, at risk for iron deficiency, should be supplemented with iron in order to achieve iron sufficiency and optimize their outcomes. Iron status should be carefully monitored, particularly in infants with specific infectious risks, risks for iron overload, or conditions affecting oxidative protections (such as glucose-6-phostphate dehydrogenase deficiency).

2. Iron formulations

2.1. Enteral iron

Human milk is relatively low in iron, but the iron present is readily absorbed due to the presence of lactoferrin. This is in contrast to neonatal formulas, where absorption ranges from less than 5 % in casein-predominant formulas, to ~7 % in soy formulas, to ~40 % in whey-predominant formulas.[16, 17] The calcium content of the milk also affects absorption. In term infants, prenatal iron accretion typically is able to offset the low iron content of breastmilk until complimentary foods are introduced around 6 months of age [9,18]. However, some studies have suggested that most infants in the US do not ingest sufficient iron-containing complimentary foods to achieve sufficiency [19]. Based on this, supplementation of exclusively breastfed infants with either iron-fortified formula or as a medicinal supplement is recommended [9]. All infant formula in the US contains iron per national guidelines, which delivers approximately 2 mg/kg/day of iron based on a daily intake of 150 ml/kg/day [20]. However, for preterm infants or those with higher iron needs, this intake is likely insufficient to meet the daily requirements, therefore medicinal iron supplements are recommended.

2.1.1. Ferrous sulfate

Ferrous sulfate is an inexpensive, commonly used medicinal iron supplement used throughout the world. It is an iron salt that provides ionic iron, Fe2+. Although enteral iron supplements have been associated with gastrointestinal upset in adults, this has not been clearly seen in neonates, though further studies are needed [21].

2.1.2. Iron gluconate

Iron gluconate (or ferrous gluconate) is a ferrous iron salt that can be administered either enterally or parenterally. Studies comparing the use of ferrous sulfate versus gluconate are limited and therefore either formulation may be used depending on hospital formulary and availability. Parenteral administration is not recommended in neonates and often avoided in pregnant women due to its preservative content.

2.1.3. Enteral iron dose

In addition to the timing of iron supplements which will be discussed subsequently in this chapter, the appropriate dose of enteral iron supplements is an area of ongoing debate. The total body iron content of a full term neonate is approximately 75 mg/kg, with the majority of this accumulated during the third trimester of pregnancy at a rate of approximately 1.6–2 mg/kg/day [20]. Assuming an absorption of enteral iron of approximately 30 %, to mirror in utero accretion rates, a daily intake of approximately 6 mg/kg/day would be required. However, due to the differences in iron absorption and iron demand after birth, this dose may not be appropriate, so individualization of dosing is recommended for each child.

Iron absorption can be affected by such factors as inflammation, milk type and calcium concentration in milk, while iron demand is affected by such factors as phlebotomy losses, changes in erythropoiesis, and red blood cell transfusions. Several trials have shown that with iron supplementation up to 6 mg/kg/day in preterm infants, some infants remain iron deficient in comparison to their term counterparts [22]. The benefit of higher iron supplementation was demonstrated in a study in which infants receiving up to 14.7 mg/kg/day of enteral iron showed continued positive impacts of supplementation on neurodevelopment, though the majority of infants in the trial received much lower doses (IQR 2.1–5.8 mg/kg/day) [23]. Iron requirements change with gestational age, postnatal age, growth rate, iron stores present at birth, medications the child is receiving such as erythropoietin or darbepoetin, and phlebotomy losses. Given the importance of iron sufficiency on long term neurodevelopment, it is important to get this right by following sequential iron studies. While the appropriate frequency of iron monitoring is not clear, at the University of Washington NICU, iron indices are monitored every 2 weeks to allow for recognition of iron deficiency/overload and adjustments of supplementation as necessary.

2.2. Parenteral iron

For infants who are NPO or for those who are unable to achieve iron sufficiency using enteral iron, parenteral forms of iron are available. Potential advantages of these formulations are that they may avoid potential detrimental effects of iron on the gut microbiome and may be more effective, particularly for infants with an upregulation of hepcidin (an acute phase reactant and the primary regulator of iron absorption) [2,24], though studies are not yet conclusive. Further, while enteral formulations contain small quantities of preservatives (such as alcohol/benzyl alcohol, sodium benzoate, potassium sorbate and/or sodium bisulfite, depending upon formulation), the majority of intravenous formulations do not. Over the last decade, several slow-release preparations have come on the market, allowing for correction of iron deficiency with fewer, larger doses [25]. For example, iron deficiency in pregnant women can now be treated with a single dose of 1000 mg/kg IV instead of 5 doses of 200 mg/kg IV [26]. As IV iron may not be compatible with total parenteral nutrition, doses can be given over 30–60 min, minimizing the risk for hypoglycemia.

2.2.1. Iron sucrose ***(Venofer)***

Iron sucrose supplies Fe(2+) via intravenous (IV) infusion with a short half-life of 6 h (VenoFer package insert). While it has been extensively used in both pediatric and adult populations for treatment of iron deficiency, practically, its use in neonates is limited by the need for IV access for multiple repeat doses.

2.2.2. Low molecular weight iron dextran (LMW-ID)

Popularized predominantly in pregnant individuals and those with chronic iron deficiency needs (such as chronic kidney disease, inflammatory bowel disease and oncologic patients), slow-release iron formulations such as low molecular weight iron dextran, ferumoxytol and iron carboxymaltose have the potential advantage of being able to be given safely at higher doses with slow release over time, thus minimizing the pro-oxidant effect of a larger parenteral iron infusion dose [27].

Iron dextran is approved by the US Food and Drug Administration (FDA) for the treatment of iron deficiency in children 4 months of age and older and adults. However, as with many medications in the NICU, it

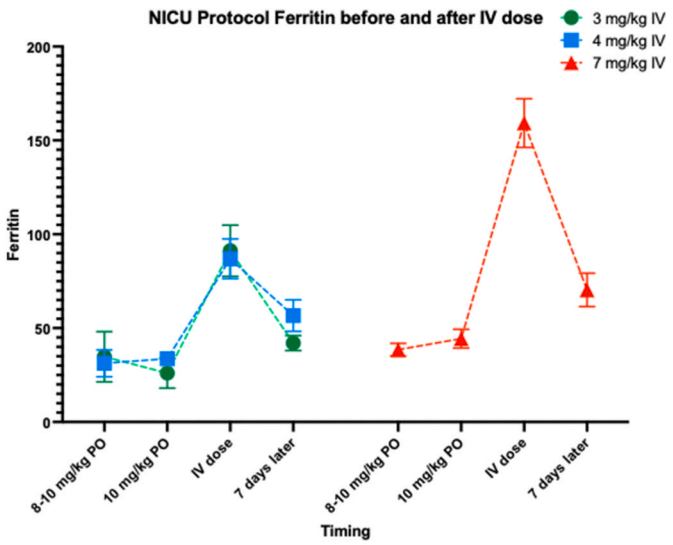

Fig. 1. Ferritin values for infants admitted to the UW NICU who received 3, 4 and 7 mg/kg/dose of IV iron following low ferritin values on up to 10 mg/kg/day of enteral iron supplements.

is used off label for the treatment of neonates. It is comprised of ferrous iron bound to a polyglucose dextran which is slowly degraded by the body, resulting in the release of Fe(2+). It has been used effectively to treat pediatric patients with iron deficiency arising from a variety of causes [28]. Similar to other IV iron formulations, it has been associated with hypersensitivity reactions in a minority of patients.

2.2.3. *Ferumoxytol*

Ferumoxytol (FMX) is an iron oxide with a carbohydrate shell originally implemented as a magnetic resonance imaging (MRI) contrast agent. The FMX particle is originally taken up by the reticuloendothelial system and stored in lysosomes. Over time, the carboxy-methyl-dextran coating is cleaved and the iron core is then incorporated into the body's iron stores.

The majority of studies examining the use of FMX for treatment of iron deficiency are in adults, however, there have been some trials examining its use in children. In a study by Hassan et al. [29], subjects ranging in age from 1 month to 19 years were given 10 mg/kg/dose. Iron parameters measured at 1 and 4 weeks showed improved iron status. Initial rapid administrations of FMX were found to be associated with hypersensitivity reactions, however these were ameliorated with slower administration times and pretreatment with diphenhydramine. To our knowledge, no studies exist examining this formulation specifically in preterm infants, though it is being used in an ongoing trial at the University of Washington (NCT05340465).

2.2.4. *Iron carboxymaltose*

Iron carboxymaltose is another slow-release IV iron formulation used most commonly in adults. However, it has been used effectively off label for pediatric patients for treatment of iron deficiency with a good safety profile. Powers et al. completed a retrospective review of the efficacy and tolerance of iron carboxymaltose since their adoption of this medication for treatment of children with iron deficiency who responded poorly to oral iron. In their cohort of 72 patients ranging in age from 9 months to 18 years, they found that iron carboxymaltose was effective in achieving an increase in hemoglobin values when assessed 4–12 weeks after the initial infusion with only minor transient complications encountered in a minority of patients [30]. A side effect of iron carboxymaltose is hypophosphatemia [31], so safety in preterm infants must be established before routine use.

2.2.5. *Parenteral iron dose*

Due to the risk of free iron and potential oxidative injury with higher parenteral iron doses [27], clinicians must balance the goal of relieving iron deficiency with as few IV doses as possible (to decrease the need for IV access) with avoiding high doses that could lead to pro-oxidant injury. Because of the short half-life and need for multiple doses, use of iron sucrose is suboptimal given the newer long-acting preparations available. The relatively slow-release IV iron formulations (such as LMW-ID, ferumoxytol and iron carboxymaltose) potentially overcome this barrier, allowing higher doses to be given less frequently. No standard dose has been approved for neonates, though doses of up to 25 mg of iron are approved for pediatric patients who receive LMW-ID. At our institution, LMW-ID is used as our standard IV iron formulation for infants who are either NPO or who are iron deficient despite oral iron supplements of 10 mg/kg/day. When we initially transitioned from iron sucrose to LMW-ID, doses of 3 mg/kg/dose were used. However, we have increased this standard dose step-wise to 7 mg/kg/dose based on retrospective review of our local data (Fig. 1).

3. Timing of iron supplements

The appropriate timing of initiation and decrease/cessation of iron supplements in iron deficient neonates is a topic of ongoing controversy. Animal and clinical trials have identified late pregnancy and the early perinatal period to be particularly vulnerable to the long-term neurodevelopmental effects of iron deficiency. Based on this, achieving optimal iron status is critical to neuroprotective care in the early newborn period in preterm infants [1]. However, this must be balanced with the potential oxidative effects of free iron in newborn preterm neonates with immature anti-oxidant mechanisms [32]. Most regulatory agencies therefore err on the side of caution and recommend initiating iron supplementation in preterm infants beginning at 2–4 weeks, and later in those with anticipated adequate prenatal stores, including term exclusively breast-fed infants [9,11].

However, a recent secondary analyses of infants born 24–28 weeks' gestation suggested that the greatest positive neurodevelopmental impact of iron supplementation occurred during the early postnatal weeks (<29 weeks postmenstrual age), with efficacy diminishing as term gestation approached [23,33]. At our institution, we therefore initiate iron supplements beginning at one week after birth to optimize iron sufficiency within the critical neurodevelopmental window. We target a ferritin level of >75 mg/L based on normative fetal developmental studies, and studies showing adverse neurodevelopmental outcomes with iron deficiency [23,34]. This approach is designed to mimic the placental transfer of iron during the third trimester.

A significant knowledge-gap exists regarding how to manage iron during the transition from prematurity to infancy. Lorenzo and others established normative values for ferritin during gestation, suggesting that ferritin <75 ng/mL was consistent with mild iron deficiency, and <40 ng/mL was severe iron deficiency. Yet normative ferritin values for one year-old infants range upwards of 12–24 mg/L. Little is known about when this transition occurs, or how to best manage iron supplementation during this time. Currently, the AAP, CDC and ESPGHAN all recommend continuing low-level iron supplementation until 12 months of age in preterm infants and those at risk for iron deficiency, such as infants fed an exclusive breastmilk diet who do not receive adequate iron intake from supplementary foods. However, as noted above, in the secondary analysis of enteral iron supplements in extremely preterm infants receiving up to 12 mg/kg/day of iron supplementation, the positive association between oral iron and 2-year Bayley Scales of Infant Development (BSID-III) scores diminished and reversed with corrected gestational age, with an inflection point around 36–37 weeks postmenstrual age [33]. We infer from these data that supplementing iron to target the fetal level of 75 ng/mL is likely not necessary after 36–37 weeks postmenstrual age, and may even be harmful. Based on these findings, we have adjusted our local guidelines to decrease the target

ferritin value to 24 ng/mL beginning at 36 weeks postmenatrual age for all infants on iron supplementation (at our institution, this would be infants born <34 weeks' gestation or with perinatal risk factors for iron deficiency).

4. Iron monitoring

In this review, we have summarized the importance of targeting optimal iron status to improve hematologic and neurodevelopmental outcomes, with both excess and insufficient iron being detrimental. To achieve this delicate balance, serial monitoring of iron parameters is indicated.

4.1. Hemoglobin and hematocrit

Historically, the most commonly used iron indices were hemoglobin (Hb) and hematocrit (Hct), with iron deficiency and iron deficiency anemia considered synonymous. However, several robust animal and clinical trials have shown that pre-anemic iron deficiency is associated with long-term neurodevelopmental harm [35]. In order to sustain oxygen carrying capacity, iron is prioritized for red blood cell production during times of deficiency [36]. Therefore, tissue-level iron deficiency, including brain iron deficiency, may precede changes in hemoglobin and hematocrit. Further, given the high rate of transfusions in preterm neonates, and the change in normative values over gestation [37], hemoglobin and hematocrit are unlikely to adequately reflect total body iron status. We therefore propose that hemoglobin and hematocrit are poor surrogates for total body iron status, particularly in neonates.

4.2. Ferritin

Beyond hemoglobin and hematocrit, ferritin has a longstanding history as the default iron metric. Because of this, the most robust data examining thresholds for iron sufficiency are established with ferritin values, ferritin values of <75 ng/mL are generally considered to suggest iron deficiency for preterm infants [34]. Ferritin values normally fall after birth and values of less than 13–24 ng/mL are considered to reflect iron deficiency around the first year of life [38].

Ferritin is the storage form of iron and therefore low values reliably reflect inadequate iron for storage. However, ferritin is an acute phase reactant, upregulated in the setting of inflammation, so elevated values may falsely suggest iron sufficiency. Based on this and more recent markers having superior phlebotomy and price indices, ferritin is becoming less commonly used in the NICU [39].

4.3. Zinc protoporphyrin-to-heme ratio (ZnPP/H)

In the absence of sufficient iron, which is typically required to form heme (H), zinc can be incorporated into the protoporphyrin ring to form zinc protoporphyrin (ZnPP). When iron availability is low, the concentration of ZnPP increases, resulting in a higher ZnPP/H ratio. Therefore, a high ZnPP/H value is indicative of iron deficiency. An advantage of this biomarker is that it is less affected than ferritin by inflammation [40]. However, in transfused infants, the ZnPP/H value may be affected by the ZnPP/H content of adult transfused cells. Also, as the ZnPP/H value reflects that of the entire red cell mass, as opposed to nascent red blood cells, ZnPP/H may be slow to respond to acute changes in iron status.

Table 1
Enteral and parenteral iron formulations commonly used in the NICU.

Enteral Iron Supplements	Parenteral Iron Supplements
Ferrous sulfate	Iron sucrose
Iron gluconate	Low molecular weight iron dextran (LMW-ID)
	Ferumoxytol (FMX)
	Iron carboxymaltose

4.4. Reticulocyte hemoglobin equivalent (Ret Hb)

The reticulocyte hemoglobin equivalent (Ret Hb) refers to the hemoglobin content of red blood cells recently released from the bone marrow, termed reticulocytes. It carries several distinct advantages in comparison with other serum markers: 1) It specifically measures hemoglobin (and thus iron) content in newly formed red blood cells via fluorescence flow cytometry, and therefore reflects the iron status of the past 5–7 days. 2) Animal studies have found that Ret Hb changes may predate changes in brain iron status [41]; 3) It can be measured along with the reticulocyte count on most CBC analyzers without the need for additional phlebotomy, thus saving blood and cost. Based on these significant advantages, Ret Hb has become a broadly used measure of iron status in NICU's throughout the US [39]. A disadvantage, however, is that while some early studies have identified potential target thresholds for the neonatal population [37,42], these have not yet been correlated with long-term outcomes. At our institution, we target Ret Hb values above 28 pg to indicate iron sufficiency in the neonatal period.

4.5. Other emerging measures

Emerging studies have aimed to identify alternative or complimentary markers of iron status in neonates, with an emphasis of limiting phlebotomy. Point of care ferritin measures and potential urinary markers, such as ferritin and hepcidin, have been identified, though these are not available in clinical practice and have not yet been widely validated in the preterm population [43,44]. The association of additional complete blood cell count (CBC) parameters, including the reticulocyte hemoglobin measure, are also an area of ongoing research with the aim of capitalizing on blood drawn already as part of a CBC [45].

5. Contraindications to iron supplementation

Although most preterm and term infants affected by certain perinatal risk factors are at risk for iron deficiency, there are some conditions in which iron supplementation is contraindicated. The most common situation occurs with the multiply transfused infant in the absence of phlebotomy loss. For the most part in the NICU, red blood cell transfusions are given to counteract the effects of phlebotomy losses [46]. In these scenarios, ongoing iron supplementation is safe and should be continued if indicated by iron status parameters. This is because the iron housed in red blood cells has been lost from the body as phlebotomized blood. However, in cases of hemolysis, such as Rh or ABO incompatibility, disseminated intravascular coagulation, thalassemias, G6PD or sickle cell anemia where the red blood cell components remain in the body, transfused red cells add to the total body iron load and therefore supplemental iron is not indicated.

Another contraindication to iron supplementation is sepsis. Some bacteria, in particular gram-negative bacteria, are siderophilic. Iron supplementation in infants with active infection with gram negative bacteria should thus be avoided. Pervasive iron supplementation in regions where malaria is endemic has been associated with worse outcomes and therefore consideration regarding the risks and benefits of supplementation should thus be considered in these specific environments [14].

Finally, iron supplements should be targeted to an individual's iron status. In cases of iron overload (typically defined as ferritin values above 350–400 ng/mL), iron supplements should be paused [47]. Infants with disruptions of iron absorption and utilization are at particular risk, such as those with hemochromatosis, gestational alloimmune liver disease (GALD) and certain inborn errors of metabolism (see Table 1).

Table 2
Outstanding questions in neonatal iron research.

Iron Research Agenda
1. How to best measure brain iron status?
2. Can we measure iron non-invasively?
3. How do we supplement iron most safely and effectively?

Practice points

- Optimizing iron status is a critical component of neuroprotective care in the NICU
- Sequential monitoring of iron status of those at risk for iron deficiency and/or overload is needed to balance adequate supplementation with the risk of iron excess.
- Maximizing iron status using delayed cord clamping and limited phlebotomy will help optimizing iron sufficiency.

Research agenda

- How to best measure brain iron status?
- Can we measure iron non-invasively?
- How to we supplement iron most effectively?

6. Outstanding questions

Iron optimization in neonates is an ongoing area of active research. Several independent investigators as well as work groups throughout the world have been established to address this topic with the specific goal of improving iron status for at-risk neonates (International Society of Blood Transfusion, Neonatal Hematology and Transfusion Medicine (NeoHeaT)). In our view, several key outstanding questions remain, which are summarized in Table 2.

Given the irreversible effects of brain iron deficiency in the neonatal period, ensuring optimal brain iron status during this critical period is essential to effective neurocritical care for neonates. However, as iron is prioritized for oxygenation and erythropoiesis over the brain, most hematologic indices fail to recognize when the brain is iron deficient prior to its effects on erythropoiesis [36]. Animal studies suggest that Ret Hb changes may predate brain iron deficiency [48], however a study on the correlation between this marker (or alternative markers) and neurodevelopmental effects is needed. Additionally, current thresholds for iron deficiency most commonly reflect gestational age specific norms-instead, values that optimize neurodevelopmental outcomes are needed to guide iron supplementation in the neonatal period.

Iron lost through phlebotomy is likely the primary cause of iron deficiency in hospitalized neonates. Therefore, a non-invasive measure of iron status would be an ideal way to both minimize iron loss and minimize painful procedures which are in themselves associated with adverse outcomes. There have been some early studies evaluating urinary measures of iron status, though these have not yet been validated broadly [43,44].

Although enteral supplements are considered the standard of care for most iron deficient infants, the potential advantages of IV iron supplementation have been highlighted in other populations, such as pregnant people [26]. In addition to potentially achieving iron sufficiently more quickly, IV iron also bypasses the enteral route. Some studies have suggested that excess enteral iron may have adverse impacts on the intestinal microbiome [49,50]. Thus, IV iron has potential advantages over enteral supplements, though these potentials must be evaluated in the neonatal population prior to widespread use. This question is currently being addressed in an NIH-funded prospective, randomized trial at the University of Washington (NCT05340465).

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Declaration of competing interest

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Very well communicated. Easy read. Thank you.

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