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Post-discharge iron requirements of the preterm infant

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The preterm infant has a far wider range of iron status than the typical term infant, which makes it difficult to estimate post-discharge iron requirements. Preterm infants are typically born with lower absolute iron stores than term infants and are subjected to multiple factors in the neonatal intensive care unit (NICU) that can influence iron balance positively and negatively. As a result, preterm infants can be in neutral, positive or negative iron balance at the time of hospital discharge. It is from this base that their post-discharge iron requirements must be calculated. One must also consider variations in post-discharge growth rates because rapid growth increases iron requirements. The preterm infant at discharge may have a 40% higher growth rate than a similarly post-conceptionally aged term infant as they catch up from the almost inevitable growth restriction that occurs in the NICU. An important aspect of any postdischarge iron management plan is monitoring iron status in the first year of postnatal life.

FACTORS THAT DETERMINE IRON STATUS OF PRETERM INFANTS AT HOSPITAL DISCHARGE

The fetus accretes the majority of the total body iron present at birth during the last trimester (1). Iron is actively transported from the maternal to the fetal circulation across the placenta (2). This process maintains a total body iron content of approximately 75 mg per kg fetal body weight throughout the third trimester (1). Thus, an extremely low birth weight infant (LBW) who weighs 500g at birth has only 37.5 mg of total body iron, and the appropriate

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for gestational age term infant who weighs 3.5 kg at birth has 262.5 mg. Iron is distributed among three body compartments: red blood cells, storage pools, and non-red cell tissue iron. The vast majority of the 75 mg/kg of total body iron is found in the red blood cells. This compartment contains approximately 55 mg/kg and is indexed by the hemoglobin and hematocrit concentrations. The storage pools, mostly found in the reticulo-endothelial system in the liver, contain 12 mg/kg of total body iron and are best indexed by the serum concentration of the iron storage protein, ferritin (see also Hernell et al, this Supplement). Ferritin concentrations increase slightly with gestational age from 24 to 40 weeks. The mean value at term is 170 $\mu\text{g/L}$, with a 5th percentile cut off of 59.8 $\mu\text{g/L}$ (3). Ferritin concentrations are considerably higher during the first months of life than in older infants and toddlers (4–6), and term infants have greater iron stores per unit body weight than children or adults (4–6). Although the tissue pool is the smallest, accounting for only 8 mg/kg, it is important because iron in that pool is required for cellular metabolism. Iron-containing hemoproteins and enzymes are critical for intracellular oxygen delivery, oxidative phosphorylation and, in the brain, neurotransmitter synthesis. Unlike the other two pools, there are currently no biomarkers that assess tissue iron status. This is unfortunate because much of the symptomatology of iron deficiency, including the risk to neurodevelopment, is due to the depletion of iron at the tissue level (7, 8).

Certain common gestational conditions compromise fetal iron status, and other, much rarer conditions cause iron overload. These conditions are important to consider because they alter the baseline iron status from which the preterm infant begins life in the NICU where a large number of events can further perturb iron balance. Severe maternal iron deficiency anemia, intrauterine growth restriction (IUGR), maternal hypertension (without IUGR), pre-gestational or gestational maternal diabetes mellitus, and maternal smoking decrease fetal iron stores (4). IUGR is of particular importance in determining the iron status of the preterm infant because IUGR due to maternal hypertension is a factor in a large percentage of preterm births. Congenital hemochromatosis is a poorly understood condition that results in fetal iron overload with ferritin concentrations far exceeding 381 $\mu\text{g/L}$ (the 95th percentile at term) (9). Multiple blood transfusions can also cause iron overload in preterm infants, resulting in ferritin concentrations that exceed 1000 $\mu\text{g/L}$.

Following birth of the preterm infant, factors that result in negative iron balance include phlebotomy losses, late onset of enteral iron supplementation, low doses of enteral iron, treatment with recombinant human erythropoietin (Epo), and rapid postnatal growth. Phlebotomy losses are a major factor in a condition loosely termed “anemia of prematurity” (10). Each gram of hemoglobin lost through phlebotomy results in a loss of 3.46 mg of elemental iron. Phlebotomy losses of 10–40 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{week}^{-1}$ occur commonly in the NICU and represent a substantial loss of iron. An expert international panel recommends starting enteral iron supplementation in preterm infants between 2 weeks and 2 months of age (11). The rate of iron deficiency at 6 months of age is greater when iron therapy is delayed until 2 months of age (12). Accordingly, the expert panel recommends a dose of 2–3 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ (11); smaller doses appear to result in negative iron balance in the NICU. Epo therapy has been advocated as a way to reduce the need for red blood cell transfusion. However, stimulation of endogenous erythropoiesis requires more iron to be available. Failure to increase the iron dose to at least 6 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ during Epo therapy results in depletion of

iron stores (13). Finally, the role of postnatal growth rates should not be forgotten or underestimated (14, 15), particularly given the current emphasis on improving growth rates of preterm infants in the NICU for neurodevelopmental reasons (16). Rapid growth results in rapid expansion of the red cell mass, and increased hemoglobin production requires additional iron. Conversely, positive iron balance occurs with early and adequate iron therapy, minimizing phlebotomy, liberal transfusion of red blood cells, parenteral iron and slower growth rates. Positive iron balance can be beneficial, but iron overload is a risk, particularly when multiple red cell transfusions or intravenous iron is administered.

Given all of these factors that can influence iron balance positively or negatively, it is not surprising that a preterm infant can be discharged with an iron status that ranges from virtually depleted to overloaded. The status at discharge dictates subsequent iron needs after discharge. Biomarkers such as hemoglobin concentration and serum ferritin concentration at discharge can help guide post-discharge iron therapy.

THE POST DISCHARGE IRON REQUIREMENTS OF THE LOW BIRTH WEIGHT (LBW) INFANT

LBW, defined as birth weight < 2500 g, is a major public health problem and affects 14% of newborns globally. Its incidence varies between 5% in Sweden to 28% in India. LBW infants include both term, small for gestational age and preterm infants. LBW is a significant risk factor for lifelong health problems, including cognitive and behavioral dysfunction. Most LBW infants are only marginally LBW (2000–2500 g). Infants in this weight range rarely require intensive care, and clinical practice regarding iron supplementation of these infants is highly variable (17).

Two approaches can be used to estimate post-discharge iron requirements for the LBW or very LBW (VLBW, <1500g birth weight) infant. The first is a factorial method that assumes that the goal is to match the iron status of the breastfed term infant at some distal time point (e.g., 1 year of age). Because the status of the two major compartments for iron, red blood cells and storage pools, are well-documented for the term infant for the first postnatal year (18), iron requirements for the preterm infant can be calculated on the basis of discharge weight, expected growth rates, and hemoglobin and ferritin concentrations at discharge. The second approach is to make recommendations based on the few observational and interventional trials that have been reported on this subject.

The factorial approach, when one assumes a birth weight of 2000 g, an average body weight of 7.5 kg at 6 months, a blood volume of 80 mL/kg, and tissue iron of 7 mg/kg, indicates that iron stores of the marginally LBW infant would be depleted within 6 to 12 weeks after birth and that the requirement of absorbed iron from 6 weeks to 6 months is $0.12 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$. Assuming an average bioavailability of 10%, this corresponds to an enteral iron intake of $1.2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$.

A few randomized intervention trials have compared the effects of different doses of iron supplements or fortification of human milk or formula in LBW infants. One meta-analysis has shown that iron (supplements or iron-fortified formula, compared with no additional

iron) given to LBW infants with birth weights 1500–2500 g significantly reduces the incidence of anemia at 6 months (18). Most of these studies used an enteral iron dose of 2 mg·kg⁻¹·day⁻¹.

Even fewer studies have examined iron supplementation in marginally LBW infants. In a recent trial, 285 infants with birth weights 2000–2500 g were randomized to receive iron supplements [0 (placebo), 1, or 2 mg·kg⁻¹·day⁻¹] from 6 weeks to 6 months of age. A dose of 2 mg·kg⁻¹·day⁻¹ significantly reduced the risk of iron deficiency anemia (IDA) at 6 months relative to placebo (19). Thirty-six and 10% of the infants who received the placebo developed iron deficiency (ID) and IDA, respectively, but only 4% and 0% of the infants in the group that received 2 mg·kg⁻¹·day⁻¹ did. Iron supplementation at a rate of 1 or 2 mg·kg⁻¹·day⁻¹ resulted in differences in iron status, but there was no difference between the two groups in the proportion of infants who developed ID or IDA. Iron supplements did not adversely affect infant growth, infections or other morbidity. The study investigators found that an actual iron intake of 0.25 mg·kg⁻¹·day⁻¹ was sufficient to prevent IDA and an intake of 1 mg·kg⁻¹·day⁻¹ prevented ID (19). In a follow-up study, they observed a significantly higher proportion of abnormal behavioral scores at 3.5 years of age in the placebo group (20). Using a validated questionnaire (Achenbach Child Behavior Checklist), the prevalence of children with behavioral scores above the US subclinical cut-off was 12.7%, 2.9% and 2.7% in the 0, 1, and 2 mg·kg⁻¹·day⁻¹ groups, respectively, as compared with 3.2% in a reference group of children with normal birth weight. The risk of behavioral problems, adjusted for socioeconomic confounders, was 4.5 times higher (95% CI: 1.3–15.8) in placebo group when compared with the infants who received iron supplements. However, no significant differences were observed in cognitive scores.

ESPGHAN guidelines recommend giving iron supplements at a dose of 1–2 mg·kg⁻¹·day⁻¹ up to 6 months of age to infants with birth weights of 2000–2500g (21). We agree with this recommendation and, additionally, recommend a post discharge dietary iron intake of 2 mg·kg⁻¹·day⁻¹ for infants with a birth weight of 1500–2000 g. Iron supplements or intake of iron-fortified formula in the recommended doses should be continued for at least 6–12 months of age, depending on diet. Hemoglobin and serum ferritin should be checked at follow-up visits and assessed in comparison with reference levels for different ages (5, 11, 22).

THE POST-DISCHARGE IRON REQUIREMENTS OF THE VLBW INFANT

The wider range of iron status of the VLBW infant compared with the LBW infant at the time of discharge makes it difficult to recommend a single iron dosage that would cover all circumstances. The major factors that contribute to post-discharge iron status and dietary requirements in the VLBW infant include iron status at the time of discharge, dietary iron intake, and growth rate. Iron status at discharge may be influenced by dietary intake while in the NICU but will also be influenced by the number of red blood cell transfusions. Post-discharge growth rate will have a strong influence on iron demand because growth necessitates expansion of the red cell volume.

The term infant with normal iron stores at birth, who benefitted from delayed cord clamping, is breastfed, and is growing at a rate consistent with the World Health Organization standard growth curves, requires no additional iron beyond what is found in human milk (0.3 mg/L) until 4 to 6 months of age (22). However, few VLBW infants are fed exclusively human milk post discharge because of concerns for adequate protein, energy and calcium delivery. Many are discharged on human milk, often fortified with a human milk fortifier, formula and fed by bottle, or on post-discharge formulas. Currently marketed post-discharge formulas provide approximately 2.25 mg of elemental iron/kg body weight when consumed at 150 ml/kg daily.

Using the factorial method, major differences between the VLBW infant at discharge and the term infant in terms of body size, hemoglobin concentration and ferritin concentration become obvious. Whereas the term infant only needs to triple its birth weight to reach the projected goal of 10 kg at one year, the preterm infant discharged at term commonly weighs as little as 2 to 2.5 kg and thus must quadruple or quintuple its 40 week post-conceptual age weight. Nutrient volume is taken in on weight basis, and it stands to reason that this rapid growth rate will place a relatively larger stress on nutrient requirements, including iron. Furthermore, most VLBW infants leave the NICU with lower hemoglobin concentrations than term infants because of anemia of prematurity and phlebotomy-induced anemia coupled with relatively restrictive transfusion practices (10). With that in mind, the VLBW infant who is discharged from the NICU at 2.0 to 2.5 kg body weight near term post-conceptual age with a hemoglobin concentration >130 g/L and a normal ferritin concentration of 140 μ g/L will have a total body iron content of approximately 150 mg and thus will have similar post-discharge requirements to the LBW infant noted in the previous section (2 mg/kg daily). However, few VLBW infants leave the NICU with such robust hemoglobin concentrations. A hemoglobin concentration of 85 g/L is far more common and places a burden of an additional 50 mg of iron to be accreted during the first year assuming normal iron stores at discharge. If iron stores are low, as indexed by a ferritin concentration at the 5th percentile (40 μ g/L) (4), an additional 30 mg of iron will need to be accreted.

Most studies of iron supplementation of VLBW infants assess whether the enteral iron strategy prior to discharge affects iron status in the NICU and, in a few cases, after discharge. A systematic review of 26 such studies that included 2726 infants concluded that infants supplemented with enteral iron in the NICU had higher hemoglobin concentrations at 6 to 9 months of age, and that dosages beyond the standard dosing of $2\text{--}3$ $\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ were not beneficial (23). A recent observational study demonstrated that the risk of ID (48%) and IDA (26.5%) was high at 12 months of age corrected for prematurity in a cohort of Brazilian VLBW infants (24). Factors that increased risk included early cow milk consumption (relative risk = 1.7) and being born small for gestational age (relative risk = 1.6) (24). Van de Lagemaat et al assessed iron status in VLBW infants (mean birth weight 1400 grams) in infants who were fed an iron-fortified formula and a variable amount of additional iron supplements (25). The group had a total iron intake from formula and supplements of 2.7 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ until 3 months corrected age and 1.2 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ until 6 months. The incidence of ferritin concentrations <12 μ g/L was only 7.8% at 3 months and 9.5% at 6 months.

In contrast, trials of iron supplementation specifically in VLBW infants post-discharge are uncommon. Griffin et al found no differences in hemoglobin or ferritin concentration at 6 months of age (3 months of age corrected for prematurity) in preterm infants with mean birth weights < 1400 grams fed formula regimens that provided 1.17, 0.86 or 0.81 mg·kg⁻¹·day⁻¹ of iron (26). Hemoglobin concentrations in all three groups attained means greater than 110 g/L by 3 months corrected age. The group fed the higher iron concentration formula achieved that milestone at 2 months corrected age, whereas the other groups did not. Moreover, the prevalence of ferritin concentrations <10 µg/L rose steadily and peaked at 14.8% at 4 to 8 months of age, indicating a negative iron balance in a subset of infants. In 2001, Friel et al examined the effects of providing infant formulas containing 3–6 or 2–3 mg of iron/kg per day for 9 months in 58 infants with an average birth weight of 1500 g (27). There was no difference in anemia or neurodevelopment at 12 months in the two groups. However, the group that received the higher amount of iron had higher glutathione peroxidase concentrations (a marker of oxidative stress), lower plasma zinc and copper concentrations, and more respiratory tract infections, suggesting that the higher iron intake resulted in adverse effects. Marriott et al reported in 2003 that VLBW infants (mean birth weight 1454 grams) managed with a preterm weaning strategy that provided a diet with more iron had higher hemoglobin concentrations at 6 months of age than control infants (28).

ESPGHAN guidelines recommend an iron intake of 2–3 mg·kg⁻¹·day⁻¹ during the first 6 months of life for preterm infants with birth weights < 1800 g (6). We recommend a post discharge dietary iron intake 2–3 mg·kg⁻¹·day⁻¹ for infants with a birth weight of < 1500 g. However, this dose should be individualized based on hemoglobin and serum ferritin concentration, measured at discharge. If the ferritin concentration is < 60 µg/L, the iron dose should be increased to 3–6 mg·kg⁻¹·day⁻¹ during a limited period. If, however, the ferritin concentration is > 300 µg/L, typically a result of multiple blood transfusions, iron supplements should be delayed.

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ABBREVIATIONS

ID	Iron deficiency
IDA	Iron deficiency anemia
IUGR	Intrauterine growth restriction
LBW	Low birth weight
NICU	Neonatal intensive care unit
VLBW	Very low birth weight

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SUMMARY

With the exception of recent studies detailing the post-discharge iron requirements of the marginally LBW infant, there is a remarkable paucity of data regarding the post-discharge iron status and iron requirements of LBW infants. Observational studies and factorial approaches suggest that VLBW infants may have iron requirements in excess of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ during their first post-discharge year in order to achieve the iron status of the full term infant at 1 year of age. Intervention studies suggest that iron intakes less than that amount may support hemoglobin synthesis. However, iron stores as indexed by ferritin concentrations suggest that the infants enter their second postnatal year with low or low-normal iron stores, and this may place them at greater risk for iron deficiency during toddlerhood. Few recommendations exist for monitoring iron status in these infants, but it would seem prudent to monitor their hematologic and iron status both at discharge and at follow-up.