Postdischarge 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 postdischarge iron requirements. Preterm infants typically are 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 postdischarge iron requirements must be calculated. One must also consider variations in postdischarge growth rates because rapid growth increases iron requirements. The preterm infant at discharge may have a 40% higher growth rate than a similarly postconceptionally 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 (LBW) infant who weighs 500 g at birth has only 37.5 mg of total body iron, and the appropriate for gestational age term infant who weighs 3.5 kg at birth has 262.5 mg. Iron is distributed among 3 body compartments: red blood cells, storage pools, and nonred 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 reticuloendothelial 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.[3] Ferritin concentrations increase slightly with gestational age from 24-40 weeks. The mean value at term is 170 μg/L, with a fifth percentile cut-off of 59.8 μg/L.[4] Ferritin concentrations are considerably higher during the first months of life than in older infants and toddlers,[5-7] and term infants have greater iron stores per unit body weight than children or adults.[5-7] 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.[8,9]

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 (IDA), intrauterine growth restriction (IUGR), maternal hypertension (without IUGR), pregestational or gestational maternal diabetes mellitus, and maternal smoking decrease fetal iron stores.[5] IUGR is of particular importance in determining the iron status of the preterm infant because IUGR because of 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 μg/L (the 95th percentile at term).[10] Multiple blood transfusions can also cause iron overload in preterm infants, resulting in ferritin concentrations that exceed 1000 μg/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."[11] Each gram of hemoglobin lost through phlebotomy results in

Epo	Erythropoietin
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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a loss of 3.46 mg of elemental iron. Phlebotomy losses of 10-40 $mg \cdot kg^{-1} \cdot week^{-1}$ 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.[12] The rate of iron deficiency at 6 months of age is greater when iron therapy is delayed until 2 months of age.[13] Accordingly, the expert panel recommends a dose of 2-3 $mg \cdot kg^{-1} \cdot day^{-1}$[12]; 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 $mg \cdot kg^{-1} \cdot day^{-1}$ during Epo therapy results in depletion of iron stores.[14] Finally, the role of postnatal growth rates should not be forgotten or underestimated,[15,16] particularly given the current emphasis on improving growth rates of preterm infants in the NICU for neurodevelopmental reasons.[17] 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 postdischarge iron therapy.

Postdischarge Iron Requirements of the 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.[18]

Two approaches can be used to estimate postdischarge iron requirements for the LBW or very LBW (VLBW; <1500 g 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 (eg, 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,[19] 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 6-12 weeks after birth and that the requirement of absorbed iron from 6 weeks to 6 months is 0.12 $mg \cdot kg^{-1} \cdot day^{-1}$. Assuming an average bioavailability of 10%, this corresponds to an enteral iron intake of 1.2 $mg \cdot kg^{-1} \cdot day^{-1}$.

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.[19] Most of these studies used an enteral iron dose of 2 $mg \cdot kg^{-1} \cdot day^{-1}$.

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 $mg \cdot kg^{-1} \cdot day^{-1}$) from 6 weeks to 6 months of age. A dose of 2 $mg \cdot kg^{-1} \cdot day^{-1}$ significantly reduced the risk of IDA at 6 months relative to placebo.[20] Thirty-six percent and 10% of the infants who received the placebo developed iron deficiency and IDA, respectively, but only 4% and 0% of the infants in the group that received 2 $mg \cdot kg^{-1} \cdot day^{-1}$ did. Iron supplementation at a rate of 1 or 2 $mg \cdot kg^{-1} \cdot day^{-1}$ resulted in differences in iron status, but there was no difference between the 2 groups in the proportion of infants who developed iron deficiency 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 $mg \cdot kg^{-1} \cdot day^{-1}$ was sufficient to prevent IDA and an intake of 1 $mg \cdot kg^{-1} \cdot day^{-1}$ prevented iron deficiency.[20] 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.[21] 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 $mg \cdot kg^{-1} \cdot day^{-1}$ groups, respectively, 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.

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines recommend giving iron supplements at a dose of 1-2 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 6 months of age to infants with birth weights of 2000-2500 g.[22] We agree with this recommendation and,