



Iron in fetal and neonatal nutrition

Raghavendra Rao ^{a,*}, Michael K. Georgieff ^{a,b}

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

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

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

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Introduction

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

spectrum of iron deficiency and iron overload disorders during this period, their pathophysiology and current management strategies.

Determinants of iron status in the fetus and neonate

The total body iron content of a newborn infant born during the third trimester is approximately 75 mg/kg; approximately 60% of this is accreted during the third trimester of gestation.¹ The distribution of the body iron is 75–80% in red blood cells (RBC) as hemoglobin (Hb), approximately 10% in tissues as iron-containing proteins (e.g. myoglobin and cytochromes), and the remaining 10–15% as storage iron (e.g. ferritin and hemosiderin). The storage iron content progressively increases and is reflected by cord serum ferritin concentrations >60 µg/L at full term.

The iron requirements after birth are influenced by the time of onset of postnatal erythropoiesis and the rate of body growth. The iron endowment at birth and iron from external,

* Corresponding author. Mayo Medical Code 39, 420 Delaware Street SE, Minneapolis, MN 55455, USA. Tel.: +1 612 626 0644; fax: +1 612 624 8176.

E-mail address: raox017@umn.edu (R. Rao).

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

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

Perinatal iron-deficiency conditions

Certain gestational conditions associated with decreased fetal iron delivery and/or increased fetal iron demand beyond the placental transport capacity can result in perinatal iron deficiency. As in other ages, available iron

is prioritized to support erythropoiesis in perinatal iron deficiency. When maternal–fetal iron delivery is inadequate for this purpose, depletion of storage and non-storage tissue iron occurs.

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

Maternal iron deficiency, with or without associated anemia, adversely affects fetal iron status. A maternal Hb concentration <85 g/L is associated with decreased fetal iron stores (cord serum ferritin <60 µg/L). More severe

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

Factors that have a negative effect:

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

Factors that have a positive effect:

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

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

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

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

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

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