Summary of Current Recommendations on Iron Provision and Monitoring of Iron Status for Breastfed and Formula-Fed Infants in Resource-Rich and Resource-Constrained Countries

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Iron deficiency is the most common micronutrient deficiency worldwide. Infants and toddlers are at special risk due to their rapid growth, resulting in high requirements for iron to meet their needs. Globally, iron deficiency is estimated to affect around two-thirds of all children and iron deficiency severe enough to cause iron-deficiency anemia (IDA) in as many as 20%-25% of preschool children.[1-3] iron deficiency occurs both in resource-rich and resource-constrained countries and varies with age. Among European infants, the prevalence of IDA is reported to be <2% during the first one-half of infancy, 2%-3% between 6 and 9 months, and 3%-9% between 1 and 3 years of age.[4] Corresponding prevalence figures for infants in the US are lacking but have been reported to range from 6.6%-15.2% for iron deficiency and 0.9%-4.4% for IDA at 1-3 years of age, depending on ethnicity and socioeconomic status.[5] Iron deficiency may impair early childhood development and cognitive function. Risk factors for IDA in infancy are low birth weight from prematurity or intrauterine growth restriction, male sex, early cord clamping, intake of large amounts of undiluted cow milk or complementary foods (CFs) of low iron content and/or bioavailability, and low socioeconomic status.[3-6]

Assessment of Iron Status

Iron is largely distributed into 3 body compartments: the red cell mass, the storage pool, and nonheme tissue iron. The fetus maintains a fairly constant level of 75 mg of total body iron per kilogram body weight throughout the last trimester, of which most (55 mg/kg) is found in the red cell mass. Each gram of hemoglobin (Hb) contains 3.46 mg of elemental iron. The storage pool is also quite large (12 mg/kg), and the remainder of the tissues account for the final 8 mg/kg.[4-7] Currently used biomarkers include Hb, hematocrit (Hct), reticulocyte count, mean red cell volume (MCV), red cell distribution width (RDW), zinc protoporphyrin (ZnPP), soluble transferrin receptor (sTfR), serum ferritin (sFt), serum iron, serum transferrin (sTf) or total iron binding capacity (TIBC), percent transferrin (Tf) saturation, and, more recently, hepcidin. Each indexes a different aspect of iron biology. Although none alone is sufficient to estimate total body iron status or diagnose iron deficiency, they can be used in combination to give a relative assessment of iron status. Importantly, many of these markers are different in the neonate than later in life and show developmental changes over the first year to 18 months.[4] Specifically, Hb, MCV, sTf, and sFt are of different magnitude in the newborn period because they reflect the unique physiology of the intrauterine environment.

The first 4 markers assess aspects of red cell iron homeostasis. Because iron appears to be prioritized to red cells during late fetal and early postnatal life,[8] changes in biomarkers that index red cell iron status tend to be a sign of far advanced disease. When these changes occur, iron stores have already been depleted, and the risk of dysfunction of organs other than red cells (eg, skeletal muscle, heart, brain, kidney) is real.

Hb and Hct

During the first 6 weeks of life, iron is shifted from Hb to iron stores because of reductions in erythropoiesis and Hb concentration, from an average 170 g/L at

AAP	American Academy of Pediatrics	IDA	Iron-deficiency anemia
CF	Complementary food	MCV	Mean red cell volume
CoN	Committee on Nutrition	RDW	Red cell distribution width
EFSA	European Food Safety Authority	sFt	Serum ferritin
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition	sTf	Serum transferrin
		sTfR	Soluble transferrin receptor
		Tf	Transferrin
Ft	Ferritin	TfR	Transferrin receptor
Hb	Hemoglobin	TIBC	Total iron binding capacity
Hct	Hematocrit	ZnPP	Zinc protoporphyrin

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birth to 120 g/L at 6 weeks of age. These changes occur as a response to the transition from an environment that is relatively hypoxic in utero compared with the oxygen-rich atmosphere after birth, a natural decline termed "physiologic anemia." Subsequently, iron is shifted back from stored iron to Hb when erythropoiesis must increase to meet the needs of the rapidly growing infant. A Hb cut-off value to define anemia based on the fifth percentile of 110 g/L between 6 and 24 months of age has been widely used,[7] although more dynamic cut-off values during infancy are now advocated with a nadir of 90 g/L at 2 months, 105 g/L from 4-24 months, and 110 g/L for those >24 months.[9] There are many causes of anemia in children, and the presence of anemia alone at the 12-month screening time point[5] does not indicate IDA without other supporting evidence of negative iron balance. However, because the majority of total body iron is found in the red cells, a significant loss of blood cells from the body (eg, bleeding) does result in total body iron deficiency.

Mean Cell Volume

Because iron is an essential nutrient for Hb synthesis, iron deficiency decreases Hb concentrations per red cell. This manifests as a microcytosis that is indexed by a lower MCV and occurs typically before the Hct starts to decline. The MCV of the neonate is higher than that of the infant and toddler. Standards for MCV have been published from National Health and Nutrition Examination Survey databases. A value of <74 fL is considered abnormal after the age of 6 months.[10]

RDW

The RDW reflects the variability in red cell size in circulation, where a high RDW indicates greater variability and a homogenously-sized cell population has a low value. As an infant with iron sufficiency develops iron deficiency, new microcytic cells are added to the older normocytic population and the RDW increases. Normally, newborns have higher RDWs than older infants because cells containing fetal Hb are larger. Standards for RDW have been published from National Health and Nutrition Examination Survey databases, and a value of >14% is considered abnormal after 6 months of age.[11]

ZnPP

When there is insufficient iron available for Hb synthesis, other divalent cations can be incorporated into the newly synthesized porphyrin ring. The most common metal ion is zinc. Thus, an elevation in blood ZnPP is seen in iron deficiency states. Values for ZnPP/heme in newborns have been reported to be around 70 μmol/mol.[12] Standards for newborns to 6-month-olds remain undefined, but after 6 months of age values greater than 80 μmol/mol heme have been used to index iron deficiency in clinical studies.[13] ZnPP is also increased by lead toxicity (which is often comorbid with iron deficiency), hemoglobinopathies, and inflammation, thereby limiting its usefulness in children. Typically, these biomarkers change before the red cell markers and, thus, could potentially be used in an anticipatory manner.

The following biomarkers do not specifically measure red cell iron status, but they are useful because they reflect physiologic adaptations to prolonged periods of negative iron balance.

Ferritin

Ferritin (Ft) is the main iron storage protein in the body. The reticuloendothelial system has particularly high amounts. Thus, most Ft is found in the liver, and sFt levels are generally thought to reflect hepatic storage iron pools. A close relationship exists between liver iron stores and sFt concentrations. Newborn infants have relatively large iron stores, and Ft concentrations in cord blood are quite high.[12,14] Shao et al[15] reported a mean value at term of 170 μg/L with the 95th and 5th percentiles being 381 μg/L and 59.8 μg/L, respectively. Postnatally, sFt values fall to adult levels by 18 months of age.[16] sFt is one biomarker for which neuro-physiologic risk cut-offs have been potentially identified in the newborn.[17] However, postnatally, the relationship between a sFt cut-off and risk for impaired brain development has not been determined. sFt concentrations will also index iron overload as seen with congenital or hereditary hemochromatosis and red cell transfusion induced overload. Because Ft acts as an acute phase reactant during inflammatory states, its usefulness as a screening tool is limited. The concern is that children with low iron stores may exhibit normal sFt concentrations if they are infected. Simultaneous measurement of a marker of inflammation (eg, C-reactive protein or α-1-acid glycoprotein) may guide interpretation of sFt.[18] Recently suggested cut-off levels to define iron deficiency are: 40 μg/L from birth until 2 months, 20 μg/L at 4 months, and 10-12 μg/L from 6 months onward.[4]

Serum Iron, Tf Saturation, and TIBC

When iron demand cannot be met by iron supplied by either diet or mobilization of storage iron, the body adapts by increasing iron-binding capacity through synthesis of Tf, the main component of TIBC. A low serum iron combined with an increase in sTf concentration results in low percent Tf saturation. sTf concentrations increase with gestational age but remain stable after term.[19] Thus, TIBC values are quite similar between birth and adulthood. The % saturation of TIBC is thought to be a main regulator of hepcidin, which ultimately regulates intestinal iron absorption and trafficking.[20]

Tf Receptors

Most cells take up iron by means of Tf receptors (TfRs) that span the outer cell membrane. Iron circulates bound to Tf, and saturated Tf has high affinity for its receptor. Intracellular iron deficiency increases membrane TfR expression. A certain percentage of TfR is shed into the serum where it can be measured as sTfR. Increased sTfR concentration is an indicator of cellular iron depletion.