

# Occurrence and Detection of Iron-deficiency Anemia in Infants and Toddlers

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Infants and toddlers are particularly vulnerable to developing iron deficiency, which can cause irreversible deficits in neurodevelopment. Children at highest risk include premature and low birth weight infants, those who are fed cow's milk rather than breast milk or formula prior to age one, and those who drink large amounts of cow's milk as toddlers. It is important to detect iron deficiency before it becomes frank anemia through the use of appropriate laboratory tests. Hemoglobin or hematocrit testing, at around age one, has been the usual screening test. These tests, however, do not become abnormally low until frank anemia has developed. Over the past decade, research has shown the assay for reticulocyte hemoglobin content to be a much earlier indicator of iron deficiency. This article provides an overview of the epidemiology, occurrence, and detection of iron deficiency and iron deficiency anemia in young children as well as a comparison of the utility of various laboratory tests.

**ABBREVIATIONS:** CHr = hemoglobin content in reticulocytes; dL = deciliter; FEP/ZPP = free/zinc erythropoietic protoporphyrin; fL = femtoliters; g = gram; ID = iron deficiency; IDA = iron-deficiency anemia; L = liter; MCH = mean cell hemoglobin; MCV = mean corpuscular volume; mg = milligrams; ng = nanograms; NRBC = nucleated red blood cells; oz = ounces; pg = picograms; RDW = red blood cell distribution width; Ret He = reticulocyte hemoglobin; SF = serum ferritin; sTfR = serum transferrin receptor; TIBC = total iron binding capacity; TS = transferrin saturation; ug = micrograms.

**INDEX TERMS:** infants; iron deficiency; iron deficiency anemia; toddlers; young children.

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## LEARNING OBJECTIVES

1. Recognize infant and toddler populations vulnerable to developing iron deficiency.
2. Describe characteristic laboratory findings evaluating infant erythropoiesis.
3. Identify variations in iron requirements from birth to age three years.
4. Describe specific laboratory tests and expected results to detect iron deficiency anemia.
5. Distinguish the sensitivity and specificity of the specific tests to detect iron deficiency anemia.
6. Recognize laboratory tests that detect iron deficiency before frank anemia develops.
7. Describe the main limitations of the reticulocyte hemoglobin content assay.

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Infants and toddlers are particularly vulnerable to the effects of anemia due to the rapid growth and development of the brain and the rest of the body from birth to age three. Pre-term and/or low birth weight infants are even more vulnerable. Although it is more common in developing countries due to nutritional deficiencies and chronic blood loss from parasitic infections,<sup>1</sup> iron-deficiency anemia (IDA) is the most prevalent anemia found in infants, toddlers and child-bearing age females in the United States.<sup>2</sup> Therefore, it is important to detect a state of iron deficiency in these patient populations before frank anemia has occurred.

**PREVALENCE AND EFFECTS OF IDA IN INFANTS AND TODDLERS**

The Centers for Disease Control and Prevention (CDC) monitor the prevalence of nutritional disorders including iron deficiency (ID) via the National Health and Nutrition Examination Survey (NHANES). Based on data collected in 1999-2000, the estimated prevalence of ID among

toddlers aged one to two years in the US was seven percent and IDA was two percent. ID was estimated to be five percent, while IDA was three percent in toddlers aged three to five years.<sup>2</sup> These rates are higher than the ID targets set by Healthy People 2010 of five percent for one to two-year-olds and one percent for three to four-year-olds.<sup>3</sup> The prevalence of ID for each of these age groups is higher

for children living in poverty.<sup>2</sup> Based on additional data collected in 1999-2002, the prevalence of ID is increasing in the United States as the Hispanic population increases. ID rates were found to be equivalent for White, non-Hispanic and Black toddlers aged one to three years at 6% each, but were higher for Hispanic toddlers at 12%.<sup>4</sup> The prevalence difference between Hispanic children versus the other two racial/ethnic groups may be due to higher incidence of obesity, not attending organized daycare, or lower socioeconomic conditions for the Hispanic toddlers.<sup>1-4</sup> Consequently, geographic areas with large numbers of Hispanic families, particularly those living in lower socioeconomic conditions, may see higher rates of IDA in toddlers.

The effects of ID in toddlers and, particularly, in infants include impaired growth and intellectual development as evidenced by lower than expected IQ scores and shorter stature. Low IQ may become irreversible by the time ID advances to the anemia level and iron therapy is begun to resolve the deficiency.<sup>5</sup> Studies have also demonstrated a higher frequency of stroke in toddlers with IDA than healthy toddlers.<sup>6,7</sup> Other potential consequences of IDA can include impaired immunity and temperature regulation, glossitis and other abnormalities of the mucosa of the mouth and esophagus,<sup>8</sup> and alterations in sleep patterns.<sup>9</sup> There is also a proven association between being iron deficient and increased lead absorption, which exacerbates impairments in cognitive development and makes these children doubly at risk for irreversible neurodevelopmental deficits.<sup>10</sup> The health goal is to detect ID as early as possible and before the development of actual anemia.

**Table 1.** Changes in erythrocyte laboratory values from birth to age three years

**Midpoint of normal range**

**Laboratory test (units)**

Age	RBC	HGB	HCT	MCV	MCH	MCHC
	(x10 <sup>12</sup> /L)	(g/L)	(L/L)	(fL)	(pg)	(g/dL)
0-1 day	5.10	190	0.58	110	36	32
2-4 days	5.16	188	0.58	108	36	32
5-7 days	5.00	178	0.57	110	36	32
8-14 days	4.80	173	0.54	105	36	32
15-30 days	4.10	151	0.46	103	34	32
1-2 months	4.20	135	0.41	95	32	34
3-5 months	4.35	132	0.43	95	30	34
6-11 months	4.40	130	0.43	90	27	34
1-3 years	4.10	126	0.41	84	27	34

RBC = red blood cell count; HGB = hemoglobin; HCT = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration.

Data derived from: Rodak BF, Fritsma GA, Doig K, editors. Hematology: clinical principles and applications, 3<sup>rd</sup> edition. St. Louis, MO: Elsevier; 2007: inside front cover "Hematology Reference Ranges–Pediatric".

### NORMAL INFANT ERYTHROPOIESIS

Substantial changes occur in the blood and bone marrow of the newborn infant within the first few hours and days after birth. Given a full-term birth (37-42 weeks gestation) and normal pregnancy, infants are born with iron stores sufficient to last until about six months of age. This is one reason why ID and IDA are more common in toddlers than in infants. Pre-term infants (<37 weeks gestation) are born with smaller stores of iron and grow at a faster rate, and are thereby at risk for IDA at an earlier age of two to three months.<sup>1,11</sup>

The bone marrow is fully active in erythropoiesis and highly cellular at birth. During the first few days of life, the peripheral blood erythrocyte count increases steadily and then plateaus for about two weeks. The erythrocyte count then slowly declines over the first year of life and levels off at about 3.40 to 5.20 X 10<sup>12</sup>/L for the next two years of life.<sup>11</sup>

The erythropoietin levels at birth are higher than adult levels but gradually drop the first few weeks after birth to near zero. This corresponds with what is called a “physiological anemia” during the second to third month of life for full-term infants or the first or second month in preterm infants.<sup>1,11</sup> The life span of erythrocytes in the infant is about 60 to 80 days as compared to 120 days in adults, and is even shorter in premature infants.<sup>11</sup>

Infants have a peripheral blood reticulocytosis of four percent to six percent at birth and demonstrate 3 to 10 nucleated red blood cells (NRBC) per 100 white blood cells. Reticulocytosis persists for about three days and then declines while NRBCs disappear from the peripheral blood. Premature infants have higher values for both reticulocytes and NRBCs than the full-term infant. Site of sampling affects the values obtained, yielding higher hemoglobin levels in capillary samples from a heel stick compared to venous samples. See Table 1 for hemogram normal range midpoint erythrocyte values during infancy to age three. Preterm and low birth weight infants have lower values than full term infants. By age one, preterm infants’ values are generally at normal levels, while low birth weight infants sometimes take longer to reach normal values.<sup>11</sup>

In infants, about 30% of required iron comes from diet, while 70% comes from recycled red blood cells. This compares to 5% and 95%, respectively, for adults. Recommended dietary allowances are 6 to 10 mg iron/day for the first year of life and 10 mg/day during ages 1 to 11 years. Iron found in breast milk, although in lower concentration than iron-fortified

cow’s milk or infant formula, has greater bioavailability and is absorbed by the infant at five times the level of absorption of the other two sources.<sup>12</sup> Exclusive breastfeeding, therefore, is recommended by the American Academy of Pediatrics (AAP) for the first six months of life<sup>13</sup> and should provide adequate iron unless the baby is preterm or low birth weight, in which case iron supplements are recommended.<sup>12</sup> According to the AAP policy statement, breastfeeding should be continued through the first year of life with gradual introduction of iron-fortified foods beginning at, but not before, six months and less than 8 oz. iron-fortified cow’s milk per day after one year.<sup>13</sup> Iron deficiency in the mother often leads to birth of an anemic newborn.<sup>8</sup>

### DETECTION OF ID AND IDA BY LABORATORY TESTING OF INFANTS AND TODDLERS

Historically, the AAP recommendation for detecting ID in full-term infants is to do the first hemoglobin level at nine to twelve months and by six months for preterm, low birth weight, and other at-risk infants.<sup>14</sup> If the hemoglobin is below 105 to 110 g/L or hematocrit below 0.31 to 0.33 L/L, a trial of iron therapy at three mg iron per kg of body weight for four weeks is recommended. A hemoglobin or hematocrit is then run and should have risen by at least 10 g/L or 0.30 L/L, respectively, to confirm ID.<sup>12</sup> The problem with this approach is that these tests do not become decreased until both storage and transport iron are depleted and frank anemia is present.<sup>15,16</sup> Recent studies show that infants with even a transient ID without anemia experience irreversible negative effects to the brain; therefore, it is important to identify an iron deficiency as early as possible.<sup>5,16</sup> Despite these studies, many clinicians still do not do a hematocrit or hemoglobin until age one or later.<sup>1,12,14</sup> Hospital laboratories do not usually see large-scale hemoglobin or hematocrit screening of infants or toddlers because most of these screening tests are performed in the pediatrician or family practitioner offices by nurses and medical assistants.

Iron studies are the typical manner in which ID is identified by laboratory testing. Typically this panel includes a serum ferritin (SF) which is the first test to decline below normal levels, though not until iron stores are depleted. The SF is an acute phase reactant and will be “falsely” elevated in patients with infections and inflammation, thereby masking a truly decreased value in ID. For this reason, SF must be tested when there is no sign of infection or inflammation in the child. Also usually included is a serum iron (SI), total iron binding capacity (TIBC), percent transferrin saturation (TS), and free/zinc erythropoietic protoporphyrin (FEP/ZPP)

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**Table 2.** Iron deficiency indicators in children<sup>8,11,14,17</sup>

Indicator/Age	Normal	Storage iron depletion	Early functional iron deficiency	IDA
<b>Serum ferritin (ug/L)</b>				
Newborn	25-200	NA	NA	NA
1 month	200-600	NA	NA	NA
2-5 months	50-200	NA	NA	NA
6 months-3 years	7-140	<7	<7	<7
<b>Serum iron (ug/dL)</b>				
Newborn	100-250	NA	NA	NA
1-12 months	40-100	NA	NA	NA
1-3 years	50-120	NA	NA	NA
<b>TIBC (ug/dL)</b>				
1-12 months	100-400	360-390	391-409	>410
1-3 years	100-400	360-390	391-409	>410
<b>% transferrin saturation</b>				
1-12 months	35-55%	15-30%	<15%	<15%
1-3 years	35-55%	15-30%	<15%	<15%
<b>FEP/ZPP (mg/dL) (hematoflourometer method)</b>				
	<30	30-99	100-199	≥200
<b>Serum Transferrin Receptor (mg/L)</b>				
1 month-3 years	<5.5	5.5-9.5	10.0-13.5	≥14.0
<b>Hemoglobin (g/L)</b>				
6-12 months	Normal	Normal	Normal	<110
1-3 years	Normal	Normal	Normal	<110
<b>MCV (fL)</b>				
6-12 months	Normal	Normal	Normal	Microcytic
1-3 years	Normal	Normal	Normal	Microcytic
<b>MCH (pg)</b>				
6-12 months	Normal	Normal	Normal	Hypochromic
1-3 years	Normal	Normal	Normal	Hypochromic

MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; NA = not available; TIBC = total iron binding capacity.

Data for this table was compiled from several sources as referenced above. These sources used varying age groupings.

level.<sup>15</sup> Most family physicians or pediatricians are hesitant to perform extensive iron studies on young children, particularly infants, due to the need for venipuncture to obtain an adequate sample. Though the FEP/ZPP can be run in the physician's office on a hematofluorometer at a fairly low cost, this test is not specific to iron-deficiency anemia.<sup>14</sup> The other tests in the iron panel become abnormal later than SF during transport iron depletion, also called early functional iron deficiency.<sup>8,15</sup> In frank anemia, SI and TS will be low and TIBC will be high. These tests become abnormal after depletion of iron stores, hence later than SF.<sup>15</sup>

The red blood cell distribution width (RDW) is a measure of anisocytosis. An increase in RDW can be an early indicator of the development of ID. The RDW, though, is calculated by two different methods, yielding different ranges and units of expression and making it less useful to clinicians.<sup>14,15</sup> Mean corpuscular volume (MCV) of red blood cells decreases below normal before the hemoglobin in ID.<sup>15</sup>

Transferrin is the carrier protein for absorbed iron. As available iron decreases, the number of transferrin receptors on the red cell surface rises to maximize the use of available iron. Some of these transferrin receptors on reticulocytes are shed in the blood in concentrations that are in direct proportion to the number of receptors on red cell surfaces.<sup>1,15</sup> The soluble (or serum) transferrin receptor (sTfR) assay is an early indicator of ID, but it is usually available only in large reference laboratories.<sup>1</sup> The values at which different stages of ID are indicated for children are displayed in Table 2.

Iron studies which show decreased SI, SF, and TS but increased FEP/ZPP, TIBC, and sTfR indicate IDA. The most definitive test for ID or IDA is a bone marrow biopsy stained with Prussian blue, although this is of little to no value in infants and toddlers due to the need to avoid patient trauma. The ratio of sTfR to SF (R/F ratio or ferritin index) has been investigated but found to mainly be of use in differentiating IDA from anemia of chronic disease.<sup>18</sup>

A more recent laboratory test has appeared in clinical use since 2000 that shows earlier detection of ID as compared to traditional iron studies. This test is the hemoglobin content in reticulocytes (CHr) assay,<sup>16</sup> also called the reticulocyte hemoglobin (Ret He).<sup>19</sup> The test measures the mean cell hemoglobin (MCH) of reticulocytes. Reticulocytes are the earliest erythrocytes released into the peripheral blood and circulate for only one to two days under normal conditions or three to four days for anemia-related early release "stress"

or "shift" reticulocytes. Hemoglobin content in these cells is a better early measure of developing functional iron deficiency than most other available laboratory tests.<sup>20</sup>

One study of adults compared the diagnostic power of the CHr with SF and TS in 78 patients, 28 of whom were iron deficient based on lack of stainable iron on bone marrow smears. The results showed the diagnostic power of CHr to be limited in patients with a MCV above 100 fL. Upon excluding patients with a high MCV, CHr was found to be the best predictor of ID based on receiver operator character (ROC) curve analysis.<sup>20</sup> The MCV issue should not interfere with use of the CHr for infants as MCV is normally below 100 fL by six months.

A study of 202 healthy nine to twelve-month-old infants in an urban area found that a CHr < 27.5 pg was a better predictor of ID without anemia than a hemoglobin < 110 g/L. This cut-off value for CHr had a sensitivity of 83% and specificity of 72% compared to a sensitivity of 26% and specificity of 95% for the hemoglobin cut-off value.<sup>21</sup> In a study of 210 children with mean age 2.9 years, CHr < 26.0 pg was found to be the best predictor of ID and IDA compared to SF, MCV, hemoglobin, MCH, SI, and TS.<sup>22</sup> In a study of 381 adolescents with mean age 16.8 years seen in a clinic setting and using a CHr < 29.0 as the cut-off for ID, an algorithm incorporating MCV, hematocrit, and CHr increased the accuracy of diagnosis of ID and IDA compared to using only MCV and hematocrit.<sup>23</sup> CHr has also been noted as a more rapid indicator of the response to iron therapy, as CHr will return to normal levels in one to two weeks after therapy is initiated<sup>23</sup> as opposed to a small increase in hemoglobin or hematocrit which occurs in four weeks.<sup>8</sup>

Adult reference ranges cited for CHr are 24-30,<sup>24</sup> 24-36,<sup>25</sup> and 27.8-34.5 pg.<sup>19</sup> Recommended cut-off values for CHr in infants and children indicative of functional ID are <26,<sup>22,26</sup> <27.5,<sup>21</sup> <28,<sup>27</sup> or <29 pg.<sup>23</sup> Normal ranges were listed only for adults with no specific CHr ranges unique to infants or toddlers.

One problem in more widespread utilization of CHr for early detection of anemia in infants and toddlers is that there are currently only a few instruments which provide this test. The CHr is available on the Siemens' ADVIA 120 and 2120 and the Sysmex XE-2100. CHr on the Sysmex XE-2100 is referred to as "Ret He". These instruments use a nucleic acid dye to stain reticulocytes and apply dual-angle light scatter to measure hemoglobin content. The CHr is inexpensive,

usually around \$20, compared to iron studies which can cost up to \$300, depending on which tests are run.<sup>16,23</sup> The CHr is reported as part of a panel of reticulocyte results when requested on the ADVIA instruments, while the Sysmex XE-2100 can be programmed to perform the Ret He based on clinical laboratory scientist preference.

One study compared results of the ADVIA 2120 CHr to the Sysmex XE-2100 Ret He. The comparisons were run on 200 blood samples from pediatric inpatients and 126 healthy medical students. The CHr and Ret He both demonstrated good precision, and showed good correlation for the pediatric samples ( $r^2=0.88$ ) and for the normal samples ( $r^2=0.83$ ). Reference ranges derived from the healthy subjects' samples were 27.9-34.5 pg for the CHr and 28.6-36.3 pg for Ret He. The researchers did note a tendency for Ret He values to be higher than CHr when CHr was  $>30$  pg. Samples from 1500 renal dialysis patients being treated with erythropoietin also were studied for comparisons of the diagnostic power of Ret He results with traditional iron tests including SI ( $<40$  ug/dL), TS ( $<20\%$ ), SF ( $<100$  ng/ml), and hemoglobin ( $<110$  g/L). A cut-off value of 27.2 for Ret He diagnosed IDA with a sensitivity of 93.3% and specificity of 83.2% based on ROC curve analysis.<sup>19</sup>

The biggest problem in usage of CHr is similar, but opposite, to that of SF. The CHr can decrease from an infection, even when the reticulocyte hemoglobin amount is normal. So, the CHr as a screening tool for early ID must be run when the infant or toddler is free of infection. In well-child outpatient screening, this is not much of a problem, but it is problematic for hospitalized pediatric patients.<sup>16</sup>

Although it is not necessarily an early indicator of ID or IDA, the hemoglobin level will in the future be measurable by a non-invasive method. Masimo Corporation released a news alert indicating they have received FDA clearance for their non-invasive, continuous total hemoglobin monitoring system. The SpHb (TM) device will be part of the Masimo Rainbow SET technology platform and will also monitor percent oxygen saturation. In addition to total hemoglobin, the Masimo device will provide non-invasive measurement of carboxyhemoglobin and methemoglobin.<sup>28</sup> As current hemoglobin tests provide only intermittent data on a patient, the non-invasive continuous SpHb™ device may provide earlier monitoring of hemoglobin levels of infants and toddlers than by invasive laboratory tests currently in use.

## SUMMARY

With the appearance of a new laboratory test, the CHr, that can detect a state of iron deficiency much earlier than a hemoglobin or iron studies, the possibility of testing infants at an earlier age and toddlers more frequently becomes feasible. This should allow detection of an iron deficit prior to irreversible neurodevelopmental damage. With the observed rising prevalence of iron deficiency anemia in young children, it is important that early detection becomes a common outcome in pediatrics and family medicine.

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