In Brief

Anemia in Infancy

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Author Disclosure

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Anemia is the reduction in red blood cell (RBC) number, hematocrit, or hemoglobin concentration to a value >2 SDs below the age-specific mean. Anemia in infancy, which may result from increased erythrocyte loss or inadequate RBC production, raises unique considerations.

Understanding the development of the hematopoietic system may be helpful in the evaluation of neonates with anemia. Erythropoiesis begins in the yolk sac at 2 weeks' gestation, generating cells that express embryonic hemoglobin. At 6 weeks' gestation, the liver becomes the predominant site of RBC production, and the cells produced primarily express fetal hemoglobin. Not until 6 months' gestation does the bone marrow become the major site of hematopoiesis. Throughout fetal life, erythrocytes decrease in size and increase in number: hematocrit increases from 30% to 40% during the second trimester to 50% to 63% at term. In late gestation and after birth, RBCs gradually switch from the production of fetal hemoglobin to adult hemoglobin.

After birth, RBC mass normally declines in response to an increase in the availability of oxygen and downregulation of erythropoietin. RBC count decreases until oxygen delivery is inadequate for metabolic demand and erythropoietin production is stimulated again. In healthy term infants, the RBC nadir, a physiologic response to postnatal life and not a hematologic disorder, typically occurs at 8 to 12 weeks of life and at a hemoglobin level of 9 to 11 g/dL.

Preterm infants also experience a decrease in hemoglobin concentration after birth, with a decline that typically is more abrupt and more profound than in term infants, reaching hemoglobin levels of 7 to 9 g/dL at 3 to 6 weeks of age. This anemia of prematurity is likely the result of lower hemoglobin levels at birth, decreased RBC lifespan, and a suboptimal erythropoietin response, and may be more pronounced in the smallest and most premature infants. Anemia of prematurity may be exaggerated by nonphysiologic factors, including frequent blood sampling for laboratory tests, and may be accompanied by significant clinical symptoms.

Blood loss, a common cause of anemia in the neonatal period, may be acute or chronic and can result from umbilical cord abnormalities, placenta previa, placental abruption, traumatic delivery, or internal bleeding in the infant. In one-half of all pregnancies, fetal–maternal hemorrhage can be demonstrated by the identification of fetal cells in the maternal circulation. Blood also can be transfused from one fetus to another in monochorionic twin gestations. In some pregnancies, these losses can be severe.

The accelerated destruction of RBCs may be either immune or nonimmune mediated. Isoimmune hemolytic anemia is caused by ABO, Rh, or minor blood group incompatibility between the mother and fetus. Maternal immunoglobulin G antibodies to fetal antigens can cross the placenta and enter the fetal bloodstream, causing hemolysis. These disorders have a wide clinical spectrum, ranging from mild, self-limited hemolytic anemias to lethal hydrops fetalis. Because maternal antibodies may take months to clear, affected infants can experience prolonged hemolysis.

ABO incompatibility usually occurs when type O mothers carry fetuses that are type A or B. Because A and B antigens are widely distributed in the body, ABO incompatibility typically is less severe than Rh disease and is not affected by birth order. In contrast, Rh hemolytic disease occurs infrequently during the first pregnancy because sensitization typically is caused by maternal exposure to Rh-positive fetal cells around the time of delivery. With the widespread use of Rh immunoglobulin, life-threatening Rh incompatibility is now rare.

Abnormalities of RBC structure, enzyme activity, or hemoglobin production also can cause hemolytic anemia

because the abnormal cells are removed more rapidly from the circulation. Hereditary spherocytosis is one such disorder, caused by a cytoskeletal protein defect that results in fragile, inflexible cells. Glucose-6-phosphate dehydrogenase deficiency, an X-linked enzyme disorder, typically causes an episodic hemolytic anemia that occurs in response to infection or oxidant stress. The thalassemias are hereditary disorders caused by defects in hemoglobin synthesis and are classified as alpha or beta according to the affected globin chain. They range in severity from silent carrier states to fatal hydrops fetalis, depending on the type of thalassemia, number of affected genes, amount of globin production, and ratio of alpha- to beta-globin produced.

Sickle cell anemia is another disorder of hemoglobin production. Children born with sickle trait are largely unaffected, whereas those who have sickle cell disease may experience hemolytic anemia associated with a wide range of clinical effects. The onset of symptoms occurs as the amount of fetal hemoglobin declines and abnormal hemoglobin S rises, typically after 4 months of age.

Infants and young children may experience serious bacterial infections, dactylitis, hepatic or splenic sequestration, aplastic crises, vaso-occlusive crises, acute chest syndrome, priapism, stroke, and other complications. Other hemoglobinopathies include hemoglobin E, the most common hemoglobinopathy worldwide. Hemolytic anemia also can be caused by infection, hemangiomas, vitamin E deficiency, and disseminated intravascular coagulation, among other disorders.

Impaired RBC production may be the result of acquired or congenital disorders. Diamond-Blackfan anemia is a rare congenital macrocytic anemia in which the bone marrow demonstrates few erythroid precursors, although the white blood cell and platelet counts generally are normal or slightly increased. Fanconi anemia is a congenital syndrome of bone marrow failure, although it is often unrecognized until later in childhood. Other congenital anemias include the congenital dyserythropoietic anemias and the sideroblastic anemias.

Iron deficiency is a common cause of microcytic anemia in infants and children, and it typically peaks at 12 to 24 months of age. Preterm infants have less stored iron and may become deficient earlier. Infants who experience increased iron loss from frequent laboratory sampling, surgical procedures, hemorrhage, or anatomic abnormalities also may become deficient sooner. Intestinal blood loss caused by exposure to cow milk also may place infants at higher risk. Lead poisoning can be the cause of a microcytic anemia similar to iron deficiency anemia.

Both vitamin B_{12} and folate deficiency can cause macrocytic anemia. Because human milk, pasteurized cow milk, and infant formulas provide sufficient folic acid, a deficiency of this vitamin is uncommon in the United States. Of note, goat milk is not an adequate source of folate. Vitamin B_{12} deficiency also is rare but may occur in human milk–fed infants born to mothers with low B_{12} stores, especially those who follow strict vegan diets or have pernicious anemia. Malabsorptive syndromes, necrotizing enterocolitis, and other intestinal anomalies may put infants at higher risk for these deficiencies, as can certain drugs or congenital disorders.

Other disorders of inadequate RBC production may be the result of chronic disease, infection, malignancy, or transient erythroblastopenia of childhood, a transient, acquired, normocytic anemia believed to be the result of damage to erythroid precursors by viruses. Although infants can be affected, most cases occur at 2 to 3 years of age.

The evaluation of an anemic infant must include a thorough history and physical examination, with special attention to cardiovascular status, jaundice, organomegaly, and any physical anomalies. The initial laboratory evaluation should include a complete blood count with red cell indices, a reticulocyte count, a peripheral blood smear, and direct antiglobulin test (Coombs' test). These results may help to direct additional testing. Treatment will be guided by the clinical severity of the anemia and the underlying illness. Transfusions may be required to restore adequate tissue oxygenation and expand circulating blood volume, and certain clinical conditions may require exchange transfusion.

Comments: Prematurely born infants are at particular risk for iron deficiency because they have not had the benefit of a full third trimester of gestation, during which an infant born at term has been able to leach from the mother (unless she is severely depleted) enough iron to maintain sufficiency until the infant has slightly more than doubled his or her birth weight. Full-term infants, unless they are actively losing blood, are not at high risk for iron-deficiency anemia in the first months of age, but premature infants with their insufficient iron stores certainly are.

What is even more significant is the fact that when the body is depleted of iron stores, the consequences go beyond anemia. Iron is critical to a wide range of physiologic functions beyond hemoglobin's role as a carrier of oxygen. Mitochondrial electron transport, neurotransmitter function, and detoxification, as well as catecholamine, nucleic acid, and lipid metabolism all depend on iron, and its deficiency results in a systemic disorder that can have long-term consequences, especially during a time of rapid brain growth.

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