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REVIEW ARTICLE

Anemia in the newborn. Update

Anemia en el recién nacido. Actualización

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ABSTRACT

Introduction: anemia in the newborn is a serious public health problem causing infant mortality and morbidity in early neonatal life.
Objective: to update knowledge on anemia in the newborn in order to outline strategies that contribute to early, timely and accurate diagnosis and treatment.
Methods: the databases Pubmed, Cochrane Library, SCielo and the academic Google search engine were consulted in search of articles published in Spanish and English up to the present time related to the subject. We used as reference 24 articles taken as a basis for the present bibliographic review.
Development: anemia is a decrease in red blood cell mass and/or hemoglobin concentration below the second standard deviation from the mean for age and sex. It is caused by a failure in the production, loss or hemolysis of red blood cells. It is most prevalent in the neonatal period, in premature infants, whose causes may be multifactorial or in the course of other co-morbidities. The severity as well as the response to treatment increases the risk of developing even more serious diseases with repercussions on quality of life.
Conclusions: an update on neonatal anemia was developed allowing an optimal and updated management of neonatal anemia, useful for neonatology services and personnel in training.

Keywords: Infant, Newborn; Anemia; Treatment.

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RESUMEN

Introducción: la anemia del recién nacido es un grave problema de salud pública al causar mortalidad y morbilidad infantil en la vida neonatal temprana.
Objetivo: actualizar los conocimientos de anemia en el recién nacido para poder trazar estrategias que contribuyan al diagnóstico y tratamiento temprano, oportuno y certero.
Métodos: se consultaron las bases de datos Pubmed, Cochrane Library, SCielo y en el buscador Google académico en busca de artículos publicados en español e inglés hasta la actualidad relacionados con la temática. Utilizamos como referencia 24 artículos tomados como base para la presente revisión bibliográfica.
Desarrollo: la anemia es una disminución de la masa de glóbulos rojos y/o la concentración de hemoglobina por debajo del segundo desvío estándar respecto de la media para la edad y sexo. Se origina por una falla en la producción, pérdida o hemólisis de glóbulos rojos. Con mayor prevalencia en el período neonatal, en prematuros, cuyas causas pueden ser multifactoriales o en curso de otras co-morbilidades. La severidad, así como la respuesta al tratamiento incrementa el riesgo de desarrollar enfermedades aún más graves repercutiendo en la calidad de vida.
Conclusiones: se desarrolló una actualización de anemia neonatal permitiendo un manejo óptimo y actualizado de la misma, útil para los servicios de neonatología y el personal en formación.

Palabras clave: Recién Nacido; Anemia; Tratamiento.

INTRODUCTION

Anemia is a major public health problem worldwide. About two billion people suffer from anemia, 68,36 (8,8 %) million live with disability and one million deaths occur in Africa and Southeast Asia. The overall prevalence and severity of anemia in low-income countries can be as high as 50-80 % and 10-20 %, respectively. Anemia of the newborn is a serious public health problem causing infant mortality and morbidity in early neonatal life. Its prevalence is very high in sub-Saharan Africa, ranging from 23 to 66 %.[1]

According to figures from the Demographic and Family Health Survey (ENDES) prepared by the National Institute of Statistics and Informatics (INEI) in 2016, it was estimated that 43,6 % of the Peruvian population aged between six months and three years suffer from anemia, this figure being even higher in rural areas (53,4 %) than in urban areas of the country (39,9 %). Anemia is defined as a decrease in red blood cell mass below the limit for meeting the body's physiologic needs. However, practically speaking, a hemoglobin or hematocrit equal to or less than the 5th percentile for the patient's age, race and sex is used as the diagnostic threshold for anemia. Because of this, it is important to consider that, in the case of newborns, gestational age at birth is a very important factor and that there is no single cut-off point, but rather a curve of values that should be taken into consideration to diagnose whether a child is anemic or not.[2]

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Nutritional deficiency anemia is a common cause of morbidity worldwide in all age groups. It affects an estimated 1 to 2 billion people and newborns are the most vulnerable groups along with pregnant women. It is also more severe in developing countries that have inadequate iron intake, poor intervention implementation program, and poor infrastructural services for early diagnosis and treatment of anemia at the health facility level.[1]

In Cuba, this condition is a major nutritional problem affecting children from six to 24 months of age. The main cause of its occurrence lies in the diet, since dietary iron intake is insufficient in quantity and quality, with a bioavailability that does not exceed 5 %. The magnitude of the problem, combined with the functional impact of this deficiency on the quality of life, requires effective measures that contribute to its reduction.[3]

The neonatal period is the most dynamic due to the profound variations and adjustments during the transit of the fetus from dependent, hypoxic, intrauterine life to fully independent neonatal life. Although the fetus is nourished and protected by the mother, it can be influenced by maternal nutritional intake and anemia.[1]

Anemia in the newborn may be caused by failure of red blood cell production, loss of red blood cells secondary to microscopic or macroscopic hemorrhage, or due to hemolysis.[4]

Anemia in newborns constitutes a complex problem and has a particular hematologic picture due to the variation in these profiles. It can produce a severe acute life-threatening event. It also causes impaired brain development, delayed brain maturation, poor school performance and work skills in later years, growth retardation, tissue and organ hypoxia, poorer cognitive, motor and socioemotional development.[1]

Precisely, anemia in the neonatal stage constitutes one of the most important and frequent health problems, especially in risk groups such as preterm infants, whose perinatological approach is currently a priority. In the Neonatology service of the General Teaching Hospital "Abel Santamaría Cuadrado" of Pinar del Río, the only reference center for the care of children under 1500 grams and the rest of the neonatal morbidity in the first 28 days of life, this disorder is frequently presented, constituting an important health problem that conditions the need for knowledge, therefore, an updated review of anemia in the newborn was carried out with the objective of updating the knowledge for a better management of this disease. The objective of this research is to update the knowledge of neonatal anemia allowing an optimal and updated management of this disease.

METHODS

A bibliographic search was carried out in the Pubmed, Cochrane Library, SCielo databases and in the academic Google search engine in search of articles published to date related to anemia in the newborn. The terms "Newborn; Anemia; Treatment" were used. Articles in Spanish and English were used. The search resulted in the selection of 24 articles taken as the basis for the present bibliographic review, with an update rate of more than 75 %.

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DEVELOPMENT

Anemia is defined as a decrease in red blood cell mass and/or hemoglobin concentration below the second standard deviation from the mean for age and sex.[5]

In general, the diagnosis of anemia is established when a hematocrit or hemoglobin at or below the 5th percentile for the patient's age, race, and sex is observed. That said, it is important to clarify that in the case of newborns (zero- two months of age according to WHO) the diagnosis of anemia in the infant poses a diagnostic challenge since hemoglobin levels show a continuous downward curve and the 5th percentile changes according to birth weight, age, race and sex of the patient. Because of this, there are no clear cut-off points to classify newborn anemia in a clear and indubitable manner and the recommendation is that any newborn with anemia be evaluated by a neonatology specialist regardless of birth weight, age, race and sex of the patient.[2]

Understanding the development of the hematopoietic system is essential for the evaluation of newborns with anemia. Briefly, erythropoiesis begins in the yolk sac at two weeks gestation, generating cells that express embryonic hemoglobin. At six weeks gestation, the liver becomes the predominant site of red blood cell production, and the cells produced primarily express fetal hemoglobin. Until six months gestation, the bone marrow does not become the primary site of hematopoiesis. Throughout fetal life, erythrocytes decrease in size and increase in number: the hematocrit increases from 30 % to 40 % during the second trimester to 50 % to 63 % at term. In late gestation and after birth, red blood cells gradually change from fetal hemoglobin to adult hemoglobin production.[2]

The values considered normal for hemoglobin and hematocrit depend on gestational age and days of life. In general, in the first week of life, normal central hemoglobin and hematocrit values should be greater than 15 g/dL and 45 %, respectively. If we take into account gestational age, in term newborns the normal hemoglobin value on the first day of life corresponds to values between 14-20g/dl, while in preterm infants the value may range between 13,5-19g/dl.[6]

The three main causes of anemia in newborns are blood loss, decreased red blood cell production and increased erythrocyte degradation. [7]

Causes of blood loss include: prenatal (feto-fetal transfusion, feto-maternal transfusion); intrapartum (obstetric accidents, placental vascular malformations or umbilical cord vessels); postpartum (internal bleeding, excessive extractions). The lack of production can be secondary to physiological hypoplastic anemia (produced in the term newborn between six-12 weeks of life and in the premature newborn between four-10 weeks of life); congenital or secondary aplastic anemias (infectious processes, hematological). Among those caused by the destruction of red blood cells we highlight: hemolysis due to blood group and Rh incompatibility, spherocytosis or other hemoglobinopathies, infections or toxins.[6]

ANEMIA DUE TO BLOOD LOSS

Blood loss, a common cause of anemia in the neonatal period, can be acute or chronic, before or during delivery and in the neonatal period. It can be the result of placental hemorrhages such as placenta previa, placental abruption, anomalies of the umbilical cord to cite velamentous insertion, hamatoma, others such as when blood can also be transfused from one fetus to another in monochorionic twin gestations, among others. Traumatic delivery or

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internal hemorrhage in the newborn due to rupture of solid viscera, intracranial hemorrhages frequent in premature babies, asphyxia, etc. In half of all pregnancies, feto-maternal hemorrhage can be demonstrated by identification of fetal cells in the maternal circulation. In some pregnancies, these losses can be severe; however, after birth, the history, clinical and complementary findings are key to the diagnosis.[2,8,9]

Feto-maternal transfusion (FMT) is the passage of fetal red blood cells into the maternal circulation before or during delivery. In the placenta, a bidirectional exchange of cells and physiological deoxyribonucleic acid (DNA) occurs mainly at the end of pregnancy, without clinical significance. When the volume is greater than 30 ml and there is blood incompatibility, maternal isoimmunization occurs. FMT is considered massive with values greater than 80-150 ml or more than 20 ml/kg body weight, although there is no consensus. Its frequency is unknown; it is estimated at 0,2-1%. If it is acute, there is a higher risk of mortality. If it is chronic, hydropis or neurological sequelae. Diagnosis is based on the detection of fetal red blood cells in maternal blood (Klehiauer test or flow cytometry). This test is the reference method. It measures hemoglobin F in maternal blood and is positive if it is > 0,1 %. Currently, flow cytometry, which measures the number of fetal cells present in maternal blood by means of hemoglobin F-specific monoclonal antibodies, can be used. The volume of fetal blood observed in the maternal circulation is a predictor of anemia.[8,10]

ANEMIA DUE TO IMPAIRED PRODUCTION

Impaired red blood cell production may result from acquired or congenital disorders such as Diamond-Blackfan anemia, Fanconi anemia, sideroblastic anemias, and congenital dyserythropoietic anemias.[2]

Diamond-Blackfan anemia is a rare autosomal dominant congenital macrocytic anemia characterized by blockage of erythropoiesis in the bone marrow, associated with reticulocytopenia in 50 % of cases as well as a variety of congenital malformations.[2]

Fanconi anemia is an autosomal recessive congenital syndrome characterized by various congenital malformations, progressive pancytopenia and predisposition to hematological malignancies and solid tumors.[2] It results in a disease that debuts during the first year of life, characterized by the very early development of hyporenerative macrocytic anemia with selective erythroblastic marrow hypoplasia in children. It was previously known by several terms: Congenital hypoplastic anemia, Blackfan-Diamond syndrome, Aase syndrome and Aase-Smith syndrome.[11]

Blackfan-Diamond anemia is a disease characterized by a genetic deficiency in the formation of erythropoietic stem cells probably due to a defect in the receptors for erythropoietin in the erythropoietic stem cells or to an absence of BFU-E and CFU-E factors in the bone marrow. This anemia is now included in an emerging group of disorders known as ribosomopathies. Its molecular biology has been extensively explored and in more than 50 % of cases the disorder appears as a result of a haploinsufficiency of the proteins associated with either of the two ribosomal subunits, however, the mechanism by which haploinsufficiency of these proteins leads to erythroid failure, as well as the presence of some of the accompanying clinical manifestations is not yet well elucidated. Clinically, the disease is characterized by severe anemia in 10 % of cases at birth, which develops in 90 % of the remaining cases within 12 months.[11]

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For their part, sideroblastic anemias - which can be acquired or congenital - are anemias produced by poor iron utilization that are usually part of a myelodysplastic syndrome and cause a normocytic-mormochromic anemia with high dispersion of the erythrocyte distribution curve or a microcytic-hypochromic anemia with an overload of iron and serum ferritin. Congenital dyserythropoietic anemias are a group of inherited disorders characterized by the occurrence of congenital anemia secondary to ineffective erythropoiesis with late erythroblasts of heterogeneous morphological characteristics in bone marrow and the development of secondary hemochromatosis.[2]

Anemia of the newborn may also be due to other disorders of red cell production such as chronic disease, malignancy or transient erythroblastopenia of infancy, a transient acquired normocytic anemia, which is thought to be the result of damage to erythroid precursors by viruses. In fact, most infections tend to decrease iron concentrations, altering hemoglobin synthesis and producing a secondary anemia, which is why it is always important to also consider infections as part of the differential diagnosis of newborn anemia.[2]

ANEMIA DUE TO RED BLOOD CELL DESTRUCTION

The accelerated destruction of red blood cells may or may not be mediated by the immune response. Isoimmune hemolytic anemia is caused by ABO, Rh or minor blood group incompatibility between 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 broad clinical spectrum, ranging from mild, self-limited hemolytic anemias to fatal fetal hydrops. Because maternal antibodies can take months to clear, affected infants may experience prolonged hemolysis.[2]

Fetal hydrops fetalis is the abnormal accumulation of fluid in at least two fetal compartments. Its origin may be immune or non-immune. In non-immune causes, parvovirus B19 is responsible for a major part, replicates in red blood cell precursors mainly in bone marrow and fetal liver, which can cause hemolysis and red cell aplasia, can cause fetal anemia and lead to heart failure with hydrops fetalis. Currently, there are study methods to assess severe fetal compromise such as fetal anemia through Doppler by measuring the peak systolic velocity (PSV) of the middle cerebral artery (MCA), which is a highly suggestive marker of fetal anemia, Similarly, invasive tests such as cordocentesis are also available, which allow us to know the exact values of fetal hemoglobin, which guides us towards the appropriate fetal therapy in each case and improves the neonatal prognosis.[12,13]

Among the causes of pathological jaundice in the newborn are those of hemolytic origin and within them the immunological ones predominate. These manifest themselves in the first hours of life and are the consequence of an incompatibility between the maternal group and that of the newborn, being the Rh and ABO groups the most frequently involved.[4]

Hemolysis secondary to ABO incompatibility occurs in 12 % of pregnancies, the clinical picture is moderate and manifests with hyperbilirubinemia, but not with anemia or hydropis. However, ABO hemolytic disease has been described as the main cause of extreme hyperbilirubinemia and Kernicterus.[4]

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ABO incompatibility usually occurs when type O mothers carry fetuses that are type A or B. Because the A and B antigens are widely distributed in the body, ABO incompatibility is typically 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 is typically caused by maternal exposure to Rh-positive fetal cells at the time of delivery. With the widespread use of Rh immune globulin, life-threatening Rh incompatibility is now rare.[2]

Kell group incompatibility is one of the least frequent (less than 5 % of hemolytic anemias together with group C and E incompatibility). Hemolytic disease due to Kell subgroup incompatibility is an important cause of hemolysis of the newborn and is the third cause of hemolysis in the newborn after Rh and ABO incompatibility. The Kell gene is located on chromosome 7 (7q34). The Kell system was named after the first woman in whom this antibody was detected. When maternal antibodies are expressed to this antigen, it attacks erythroid progenitors and creates what is known as hypoproliferative anemia. It is called hypoproliferative because the reticulocyte count is low or normal and the hyperbilirubinemia is not as severe. Non-immunologic acquired diseases include: cytomegalovirus infection, toxoplasmosis, syphilis, sepsis, disseminated intravascular coagulation. Mutations of the erythrocyte cytoskeleton: hereditary spherocytosis, hereditary elliptocytosis, among others. Erythrocyte enzyme abnormalities: glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, alpha and gamma thalassemia and unstable hemoglobins.[4]

Abnormalities of RBC structure, enzyme activity, or hemoglobin production can also cause hemolytic anemia because abnormal cells are more rapidly cleared from the circulation. Hereditary spherocytosis is one such disorder, caused by a cytoskeleton protein defect that produces fragile and inflexible cells.[2]

Glucose-6-phosphate dehydrogenase deficiency, an X-linked enzyme disorder, typically causes episodic hemolytic anemia that occurs in response to infection or oxidative stress. G6PD is critical for the conversion of nicotinamide adenine dinucleotide dinucleotide phosphate (NADP) to nicotinamide adenine dinucleotide hydrogen phosphate (NADPH) during cellular metabolism in the pentose pathway. The conversion is critical for the production of glutathione, an important antioxidant that helps protect erythrocytes against oxidative stress. Hemolysis can occur in response to radicals and reactive oxygen species created by stressors such as infections, certain foods and drugs. Because erythrocytes carry oxygen, they are particularly vulnerable to oxidative stress. G6PD deficiency decreases the erythrocyte's ability to respond to oxidative stressors leading to the formation of methemoglobin, a condition that results in cyanosis, arrhythmias, seizures and death.[2]

The three types of triggers are infections, certain medications, and certain foods. Infection is the most common cause of acute hemolytic anemia in patients with G6PD deficiency, particularly CMV, hepatitis A and B, pneumonia or typhoid fever; at the same time G6PD deficiency increases susceptibility to infections. Medications: mainly chloramphenicol, ciprofloxacin, glimepiride, glipizide, levofloxacin, methylene blue, moxifloxacin, nitrofurantoin, nitroglycerin, phenazopyridine, primaquine, probenecid, sulfacetamide and others. Neonates with G6PD deficiency are twice as likely to develop neonatal jaundice, and jaundice may be more frequent and severe in premature neonates. Hemolytic anemia and resulting jaundice due to flavism may occur in breast-fed neonates born to mothers who ingest fava beans. The newborn will show persistent high indirect hyperbilirubinemia that can be severe, increasing the risk of kernicterus if left untreated.[7]

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Thalassemias are inherited disorders caused by defects in hemoglobin synthesis and are classified as alpha or beta according to the globin chain affected. They vary in severity from silent carrier states to fatal hydrops fetalis, depending on the type of thalassemia, the number of genes affected, the amount of globin production, and the ratio of beta-globin produced.[2]

Sickle cell anemia is another disorder of hemoglobin production. Children born with sickle cell trait are largely unaffected, whereas those with 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 decreases and abnormal hemoglobin S increases, usually after fourmonths of age.[2]

Infants and young children may experience severe bacterial infections, dactylitis, hepatic or splenic sequestration, aplastic crisis, vaso-occlusive crisis, acute chest syndrome, priapism, stroke and other complications. Other hemoglobinopathies include hemoglobin E, the most common hemoglobinopathy worldwide. Hemolytic anemia can also be caused by infection, hemangiomas, vitamin E deficiency, and disseminated intravascular coagulation, among other disorders.[2]

ANEMIA AND ITS DIAGNOSIS

The time of onset of anemia can provide guidance as to its etiology. Anemia that appears on the first day of life can result in anemia due to blood group and Rh incompatibility or hemorrhagic anemia. Anemia that appears between the second day and one month of life may be due to physiological anemia, hemorrhagic anemia, spherocytosis or nonspherocytic hemolytic anemia. On the other hand, that which appears from the first month of life to the third month may be due to physiological anemia, due to lack of folate, congenital hypoplastic anemia or anemia of prematurity. To make a correct diagnostic approach in cases of low hemoglobin and hematocrit in a newborn, we must base our diagnosis on the anamnesis and obstetric history (placental alterations, time of cord ligation, drugs, visible bleeding), family history (blood group and Rh, anemia, jaundice, biliary lithiasis, splenectomy) and complementary tests that will confirm the type of anemia.[6]

The diagnosis of anemia is usually made indirectly by measuring the hemoglobin level or hematocrit, depending on availability. In daily medical practice hemoglobin is the most commonly used diagnostic test to diagnose anemia, although in cases where a rapid diagnosis is needed and there is a lack of rapid tests, hematocrit may be an easier and more convenient alternative.[2]

Among the tests to request, we highlight the hemogram and reticulocytes, which in the first three days of life should be between 4-6 % of the total red blood cell count. They are elevated in anemias due to chronic or hemolytic losses and decreased in infections and production defects. Bilirubin is elevated in cases of hemolysis. In all cases, especially in suspected hemolysis, it is important to determine blood type and Rh along with direct Coombs' test. Other tests to be performed to determine the etiology of anemia are: morphology of red blood cells in peripheral blood, determination of fetal hemoglobin value in maternal blood, coagulation study, serological test (Toxoplasma, rubella, cytomegalovirus, herpes, parvovirus and syphilis). Imaging tests such as ultrasound (abdominal and transfontanelar) in the newborn are necessary to rule out internal bleeding.[6]

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Physiologic anemia" is usually seen at six-nine weeks of age, resulting from a dramatic decrease in erythropoiesis after birth as a result of increased tissue oxygenation and reduced erythropoietin production. For example, for term newborns, hemoglobin levels at birth (>14 g/dL) typically decrease to less than 11g/dL by six-nine weeks of age as a product of physiologic anemia (also known as "physiologic nadir").[2]

Hence, to differentiate physiologic anemia from pathologic anemia in infants, it is suggested to use the following criteria: 1) Anemia (Hb <13, 5 g/dL) during the first month of life; 2) anemia with an Hb level lower than that observed in physiologic anemia (<9,5 g/dL); and, 3) signs of hemolysis (e.g., jaundice, scleral icterus, or dark urine) or symptoms of anemia (e.g., irritability or malnutrition). If pathologic anemia is present, the differential diagnosis should include its most common causes in infants, which are: blood loss (including late umbilical cord cutting or repeated blood sampling), immune hemolytic disease (call it Rh or ABO incompatibility), congenital infection, twin transfusion, and congenital hemolytic anemia (call it hereditary spherocytosis or glucose-6-phosphate dehydrogenase [G6PD] deficiency). If hyperbilirubinemia is observed, a hemolytic etiology should be suspected. If microcytosis is observed, chronic intrauterine blood loss or thalassemia should be suspected [2].

Premature infants are often born with pathological hemoglobin levels ("anemia of prematurity") because they have impaired erythropoietin production (due to immature liver function) and their red blood cells have a shorter half-life. Therefore, they are more susceptible to the effects of physiologic anemia which occurs earlier (<six weeks of age) and is more severe. Premature infants also experience a decrease in hemoglobin concentration after birth, with the decrease typically being steeper and more profound than in term infants, reaching hemoglobin levels as low as 9 g/dL at three to six weeks of age.

This anemia of prematurity is likely the result of lower hemoglobin levels at birth, decreased red cell life and a suboptimal response to erythropoietin, and may be more pronounced in smaller, preterm infants. During the neonatal intensive care stay, anemia of prematurity may be exaggerated by non-physiologic factors, including frequent blood sampling for laboratory testing, early cord clamping for depression, and late erythropoiesis accompanied by significant clinical symptoms.[2]

Establishing the cause of anemia in a premature newborn can be challenging. Clinically, fetomaternal hemorrhage (FMH) can be difficult to diagnose; the condition often presents only after the manifestation of severe fetal anemia. FMH can be confirmed by determining the fetal hemoglobin F fraction in the mother, which is traditionally performed by the Kleihauer-Betke test (KBT). [14]

The most frequent causes of anemia in this group include: inadequate erythrocyte production due to ineffective erythropoiesis, due to insufficient erythropoietin production; shortened half-life or hemolysis, due to lower intracellular ATP and carnitine concentrations, lower enzyme activity, increased susceptibility to lipid oxidation and membrane fragmentation; blood loss: due to fetomaternal transfusion, fetoplacental, twin-to-twin and repeated extractions.[15]

NEONATAL ANEMIA AND ITS MANAGEMENT

In the first days of life, blood loss has been associated with increased morbidity, neurodevelopmental disabilities and mortality in very premature newborns, so it is important to conceive placental transfusion as blood saving and to preserve blood volume in the child from birth. In the case of term infants and newborns with moderate or severe anemia, the first

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recommendation is to prevent the need for blood transfusion. To this end, the general recommendation is to implement preventive measures such as delayed umbilical cord clamping (between one and three minutes after birth depending on the disappearance of cord beats), reduction of iatrogenic blood loss (specifically by limiting the volume and number of blood draws to a minimum), seek early iron supplementation and promote adherence to blood transfusion guidelines.

These measures are generally much more effective for preterm infants than for term infants. For example, in preterm infants late cord clamping has been associated with increased hemoglobin levels and iron stores with a decreased risk of intraventicular hemorrhage and necrotizing enterocolitis whereas in term infants these benefits are less evident and are conditional on access to phototherapy treatment for jaundice.[2,16]

Management of the anemic newborn should include a thorough history and physical examination, with special attention to cardiovascular status, jaundice, organomegaly, and any other physical abnormalities. Initial laboratory evaluation should include a complete blood count with red blood cell indices, a reticulocyte count, a peripheral blood smear, and a direct antiglobulin test (Coombs' test). These results can help direct further testing. Treatment will be guided by the clinical severity of the anemia and the underlying disease. Transfusions may be required to restore adequate tissue oxygenation and expand circulating blood volume, and certain clinical conditions may require specialized management.[2]

For term newborns with mild iron deficiency anemia, the recommendation is to offer iron supplementation, either by switching to iron-fortified formula or by initiating breastfeeding supplementation with iron drops at a dose of 3 mg iron per kg/day, subject to reassessment at four weeks. If there is a positive response, namely an increase in hemoglobin levels >1 g/dL or to a value within the normal range, it is recommended that iron drops (or iron-fortified formula) be continued for two more months and then discontinued. If receiving iron-fortified formula, it is recommended to maintain the iron-fortified formula until 12 months of age. If there is no positive response, it is recommended to check adherence to treatment and evaluate the serum ferritin concentration. A serum ferritin concentration >15 µg/L suggests that the anemia is not due to iron deficiency. Subsequently, comprehensive reassessment of all newborns who were anemic at 15 to 18 months of age is recommended because the long-term effects of anemia at a very early age include impairment of physical and cognitive development in childhood.[2]

At present, the prophylactic application of erythropoietin in the premature infant and umbilical cord milking can prevent anemia due to blood loss and its complications, the latter procedure, by favoring the transfer of a larger volume of blood than that achieved by clamping.[15]

On the other hand, the use of microanalysis, smaller amounts of blood for diagnostic tests, as well as the use of transcutaneous instruments and permanent intravenous or arterial lines for laboratory measurements have greatly reduced iatrogenic blood loss and, therefore, the need for transfusion of blood products. Similarly, adherence to blood transfusion guidelines has also been associated with a reduction in the number of blood transfusions.[2]

In FMT, treatment is classically based on restoring oxygen (O2) carrying capacity and blood volume with red cell concentrate transfusion, although sometimes this volume overload can lead to clinical worsening with fatal results. The treatment of this pathology must be carried out quickly and optimally according to the hemodynamic situation of the patient.[10]

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In very premature neonates, repeated treatments with low doses of erythropoietin have been used in the prevention of necrotizing enterocolitis without evident adverse effects, supporting that when done early and prophylactically it has multiple beneficial effects in these children, with special indication in those at risk of such disease.[16,17]

Severe anemia of the newborn is more frequent in very premature newborns than in term newborns, and its management is based mainly on red blood cell transfusion. That said, it is important to note that although the use of blood products is widespread in neonatal medicine, the evidence for their potential benefit is extremely limited. Recent studies suggest that red blood cell transfusions in neonates may increase the risk of necrotizing enterocolitis, transfer of infectious agents, bronchopulmonary dysplasia and neurodevelopmental disorders.

Hence, the controversy over the balance of risks and benefits attributable to the use of RBC transfusions is still controversial and requires further study. One of the main problems in deciding when to transfuse a newborn is the lack of a clear and consensual definition of severe anemia of the newborn.

In the absence of such a definition, different specific cut-off points for hemoglobin have been tested. Of these, one that has been gaining popularity for defining severe anemia in neonates, especially because it has already been tested in different clinical trials, is a cutoff hemoglobin level of 8 g/dL or lower. Regarding the volume to transfuse, these usually vary between 5 and 20 ml/kg. While there is still insufficient evidence to establish an optimal transfusion volume for newborns, it has been reported that volumes of 20 ml/kg are associated with a lower risk of requiring repeated transfusions.[2]

However, recent studies have found an association of severe anemia and red blood cell (RBC) transfusions with bronchopulmonary dysplasia (BPD), necrotizing enterocolitis and retinopathy in premature infants, especially the smallest ones, where a higher volume and a greater number of RBC transfusions are directly related to their severity, so medical methods should be adopted to prevent severe anemia and reduce RBC transfusions because of the risks involved.[18,19,20]

Use of the lower thresholds, 11 g/dL for critically ill infants and 7 g/dL for stable infants, will reduce transfusions, conserve blood for the most needy patients, and reduce the risks associated with transfusions. The burden of proving safety rests on anyone proposing to use higher or lower thresholds than those studied. Delayed cord clamping at birth, measures to minimize blood loss from phlebotomy, and good nutritional practices are also important means of limiting the need for blood transfusion. New tools and effective individualized and preventive decisions need to be made for each patient, especially those born prematurely.[21,22,23,24]

CONCLUSIONS

Anemia of the newborn is a complex pathology whose diagnosis and management is still in many aspects quite controversial. Therefore, it is recommended that all newborns with suspected anemia receive specialized and individualized management, assessing their health status comprehensively and receiving optimal management without triggering other complications or even negatively influencing the neurodevelopment and quality of life of children. Rare diseases can also present in daily clinical practice. We must make a correct differential diagnosis and thus ensure appropriate treatment. With this review, an update on neonatal anemia was developed allowing an optimal and updated management of neonatal anemia, useful for neonatology services and staff in training.

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Authors' contribution
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