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1

Fetal anemia: Diagnosis and management

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A B S T R A C T

Fetal anemia has been known for many years as a dangerous complication of pregnancy. Its most common causes are maternal alloimmunization and parvovirus B19 infection, although it can be associated with many different pathological conditions including fetal aneuploidies, vascular tumors, and arteriovenous malformations of the fetus or placenta and inherited conditions such as alpha-thalassemia or genetic metabolic disorders. Doppler ultrasonographic assessment of the peak velocity of systolic blood flow in the middle cerebral artery for the diagnosis of fetal anemia and intravascular intrauterine transfusion for its treatment are the current practice standards. Live birth rates as high as 95% have been reported in recent years. The additional role of intravenous immunoglobulin therapy and the long-term consequences of the condition are the subjects of active ongoing research.

Introduction

The diagnosis and treatment of the most common form of fetal anemia, hemolytic disease of the fetus and newborn (HDFN), has been at the leading edge of fetal diagnosis and therapy for decades [1]. The need to assess the fetal status in HDFN was pivotal in the development of amniocentesis as a

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diagnostic technique [2]. Liley performed the first successful fetal intraperitoneal transfusion (IPT) in 1963 with the help of fluoroscopy [3]. This was followed by attempts to cannulate a range of fetal blood vessels by an open fetal surgery approach: these were, however, mostly followed by preterm birth and perinatal loss [1]. In 1981, Rodeck and colleagues performed a direct intravascular transfusion by needling chorionic plate vessels under fetoscopic visualization [4], and in the following year, Bang and colleagues transfused two fetuses through the intra-abdominal umbilical vein under real-time ultrasound guidance [5]. The possibility of noninvasive screening for fetal anemia by Doppler ultrasound measurement of the middle cerebral artery peak systolic velocity (MCA-PSV) and refinements in treatment techniques have led to survival rates as high as 95% in recent years [6].

Etiology of fetal anemia

The most common causes of fetal anemia are maternal alloimmunization and parvovirus B19 (PB19) infection (Table 1). However, many different pathological conditions are associated with fetal anemia, including fetal aneuploidies, vascular tumors, and arteriovenous malformations of the fetus or placenta, and inherited conditions such as alpha-thalassemia or genetic metabolic disorders [7]. Fetal anemia might be associated with Down syndrome because of transient abnormal myelopoiesis, a leukemic condition that occurs in approximately 10% of infants with Down syndrome [8]. Fetomaternal hemorrhage (FMH), which may occur as an isolated acute event or as a chronic, ongoing hemorrhage, is another cause of fetal anemia [7]. Finally, it should be kept in mind that in a minority of cases, the cause of fetal anemia may not be amenable to diagnosis in utero and even postnatally [9].

Maternal red blood cell alloimmunization

Maternal red blood cell (RBCs) alloimmunization is the leading cause of fetal anemia despite standardized protocols for RhD immune globulin prophylaxis, most often due to unrecognized FMH events, inadequate dosing or missed prophylaxis for antenatal sensitizing events, poor patient compliance, absence of prophylaxis for other RBC antigens, and omission of Kell typing of blood transfusions for women of childbearing age [10].

Maternal red blood cell alloimmunization occurs when the immune system is sensitized to foreign erythrocyte surface antigens, which stimulate the production of immunoglobulin G (IgG) antibodies. These IgG antibodies can cross the placenta causing hemolysis if the fetus is positive for the specific erythrocyte surface antigens, a condition known as HDFN. The disease can result in extramedullary

Table 1
Etiology of fetal anemia (modified from Refs. [7,9]).

Alloimmunization	Anti-D, anti-K, anti-c
	Other less common antigens (see Ref. [11])
Infection	Parvovirus B19
	Cytomegalovirus
	Toxoplasmosis
	Syphilis
Inherited conditions	Lysosomal storage diseases (e.g., mucopolysaccharidosis type VII, Niemann-Pick disease, Gaucher disease)
	Diamond–Blackfan anemia
	Fanconi anemia
	Alpha-thalassemia
	Pyruvate kinase deficiency
	Glucose-6-phosphate dehydrogenase deficiency
	Congenital erythrocyte membrane disorders (spherocytosis and elliptocytosis)
Other	Aneuploidy
	Twin anemia–polycythemia sequence
	Fetomaternal hemorrhage
	Placental/fetal tumors
	Maternal acquired red cell aplasia

hematopoiesis, reticuloendothelial clearance of fetal erythrocytes, fetal anemia, hydrops fetalis, and fetal death.

Approximately 43 of the 300 RBC antigens listed by the International Society of Blood Transfusion reportedly cause HDFN, but some are more likely to be associated with hemolysis than others [7,11,12].

The introduction of Rh (D) immune globulin in 1968 has greatly decreased the incidence of fetal anemia caused by Rh (D) alloimmunization; as a result, other alloantibodies have increased in relative importance. These include antibodies to other antigens of the Rh blood group system (c, C, e, E) and other atypical antibodies also known to cause severe fetal anemia, such as anti-Kell (K, k), anti-Duffy (Fya), and anti-Kidd (Jka, Jkb) [7].

Parvovirus B19

PB19 is a single-stranded DNA virus with a particular affinity for erythroid progenitor cells, potentially leading to hemolysis, bone marrow aplasia, and, occasionally, thrombocytopenia and neutropenia. Fifth disease represents the typical presentation in children, with a low-grade fever, malaise, and a characteristic “slapped cheek” facial rash, followed by a maculopapular truncal and extremity rash. Most adults are asymptomatic or may experience polyarthralgia [13]. Nearly 65% of women of childbearing age are immune to PB19, and 1.5% of susceptible women will seroconvert during pregnancy. Typically, transmission is by respiratory droplets. The overall risk of vertical transmission is approximately 17%–33%, with the highest risk occurring before the third trimester [10]. Fetal infections are mostly asymptomatic without sequelae but may result in miscarriage, severe anemia with nonimmune hydrops, and stillbirth. The risk of fetal loss is estimated at 13% when infection occurs <20 weeks and 0.5% when it occurs >20 weeks, and approximately 3% of affected fetuses develop hydrops [10].

Twin anemia–polycythemia sequence (TAPS)

Fetal anemia can also result from a unique complication of monochorionic twin pregnancies, a condition referred to as twin anemia–polycythemia sequence (TAPS). TAPS is a form of chronic intertwin blood transfusion leading to anemia in the donor and polycythemia in the recipient, without signs of oligo-polyhydramnios as seen in twin-to-twin transfusion syndrome (TTTS). It is caused by the presence of only few minuscule (<1 mm), unidirectional arteriovenous vascular anastomoses, with sparse or absent compensatory arterio-arterial anastomoses allowing slow transfusion of blood from one twin to the other, without the hemodynamic imbalance and discordant fetal urine production, as in TTTS [14]. TAPS occurs spontaneously in 3%–5% of monochorionic twins or after laser therapy for TTTS in 2%–16% of cases [14].

Placental/fetal tumors

Placental chorioangiomas are the most common benign placental tumor; when large, they can be associated with fetal anemia. The major factors contributing to fetal anemia are: FMH; micro-angiopathic hemolytic anemia because of entrapment and destruction of fetal erythrocytes in the vascular network of the chorioangioma; and the fact that despite enhanced erythropoiesis, the fetus cannot produce enough erythrocytes to compensate for the enlarged fetoplacental intravascular volume because of the existence of an extracorporeal pool of fetal blood in the intravascular space of the chorioangioma [15]. Fetal sacrococcygeal tumors can also result in fetal anemia, with secondary high-output cardiac failure and hydrops [10].

Fetomaternal hemorrhage

Massive FMH is a rare and serious condition that can cause severe fetal anemia and death. The evolution profile of the FMH is variable; it may consist of a single episode of transplacental passage of fetal blood or of chronic hemorrhage, whether by ongoing bleeding or by repeated acute episodes. Massive FMH with fetal hydrops remote from term has been managed with serial intrauterine

transfusions; however, outcomes are variable, ranging from resolution of hydrops and live birth to intrauterine fetal death [10,16].

Diagnosis of fetal anemia

Fetal hemoglobin (Hb) values increase gradually during pregnancy; therefore, anemia may be classified according to the degree of Hb deviation from the mean for gestational age (GA) [17] or multiples of the median (MoM) for GA [10,18]. Fetal anemia can also be defined by an hematocrit of less than 30%; it appears equally reliable as using Hb levels and is often used in clinical care [19]. Hydrops typically does not develop until the Hb deficit is > 70 g/L or the absolute Hb value is < 50 g/L [20]. Fetal anemia should also be suspected in fetuses presenting with isolated effusions (ascites, pericardial effusion, hydrothorax, and skin edema) or reduced/absent movements.

The diagnosis of fetal anemia is established by fetal blood sampling (FBS). The risk of fetal loss related to the procedure is reported to be 1%–2%; however, it can be higher at earlier gestations and in the presence of fetal hydrops [7]. In fetal anemia, there is an increased blood velocity secondary to decreased blood viscosity and increased cardiac output; therefore, regardless of the etiology, fetal anemia can be detected by Doppler ultrasonography on the basis of an increase in the peak velocity of systolic blood flow in the MCA-PSV [7,10]. Although there is no strong correlation between MCA-PSV and fetal Hb concentration when the fetus is not anemic or is only mildly anemic, as the Hb decreases, the MCA-PSV increases and can be used to determine the Hb value with an adequate level of approximation [7].

Technical aspects to obtain MCA-PSV are defined by the International Society of Ultrasound in Obstetrics and Gynecology guidelines [21]. An axial section of the brain, including thalami, cavum septi pellucidi, and greater wing of sphenoid, with the circle of Willis identified by color Doppler, should be obtained. The MCA is sampled at or near its origin from the internal carotid artery. The waveform peak is measured, with the angle of insonation as close as possible to 0° (Fig. 1). Higher inter- and intra-observer variability results from angle correction and sampling of more distal regions of the MCA. The fetus should be quiescent, as heart rate accelerations and movements can alter measurements. Measurement can be performed at the proximal or distal MCA [10]. A step-by-step video tutorial is available at SMFM.org/AJOG.org [7]. An MCA-PSV of greater than 1.5 MoM is used as a screening test to identify the severely anemic fetus. In nonhydropic fetuses at risk for anemia, sensitivity of a single value of MCA-PSV is reported to be 75.5%–95% for moderate or severe anemia, with a false-positive rate of 10%–12% [18,22]. After 35 weeks of gestation, the false-positive rate appears to be higher [23]. The use

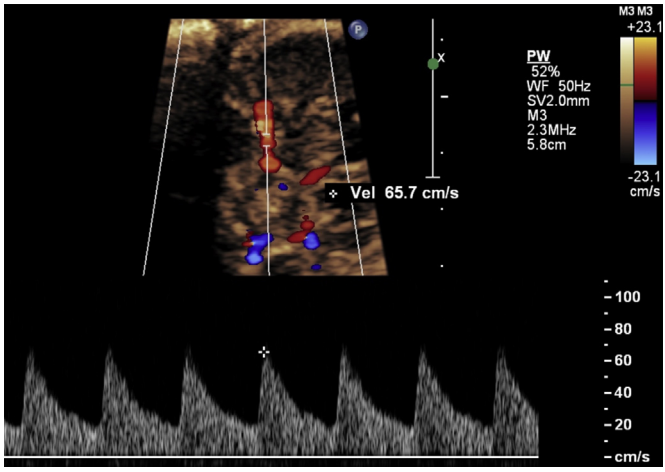

Fig. 1. Middle cerebral artery (MCA) Doppler shift waveform. The pulsed-wave Doppler gate is positioned at the proximal third of the MCA, close to its origin in the internal carotid artery. The insonation angle is near 0°.

of the MCA-PSV trends (as opposed to a single measurement) may decrease the false-positive rate to less than 5% [23]. In another study of alloimmunized fetuses at 34–37 weeks, the sensitivity of MCA-PSV alone for fetal anemia was 69% but increased to 94% when also considering signs of hydrops [24].

Presently, FBS for the diagnosis of fetal anemia is scheduled if MCA-PSV measurement is greater than 1.5 MoM and trending upward. It is performed as part of pretherapeutic assessment with packed red blood cells available for transfusion at the same time. Recommended investigations for the evaluation of suspected fetal anemia are reported in Table 1. The first manifestation of hydrops secondary to fetal anemia is usually ascites, followed by placental thickening and hepatomegaly; associated pleural or pericardial effusions are rare [10]. MCA-PSV assessment can detect anemic fetuses before the development of fetal ascites, thereby allowing to perform intrauterine transfusion before the occurrence of hydrops. Several studies have demonstrated worse outcomes following intrauterine transfusion in hydropic compared with nonhydropic fetuses [10].

Maternal alloimmunization

Pregnancies at risk are identified on the basis of a previous history of HDFN or when causative antibodies are identified on routine maternal blood group screening. If paternity is certain, initial management involves determining the paternal RBC antigen status and zygosity. If the father is heterozygous for a particular RBC antigen, the fetus has a 50% risk of inheritance and fetal genotyping can be performed. If the father is homozygous, all fetuses will inherit that antigen and genotyping is unnecessary. Fetal RhD genotype can currently be reliably determined using cell-free DNA in the maternal plasma. Experience with this approach is extensive, with prediction accuracy and test sensitivity approaching 100% and very few false-negative results [25]. The International Blood Group Reference Laboratory in Bristol, UK, currently performs genotyping for RhD, Rhc, RhC, and RhE after 16 weeks and for Kell after 20 weeks of gestation [10]. In sensitized pregnancies, serial titers are performed, typically every 4 weeks until 28 weeks of gestation and every 2 weeks, thereafter. In the past, once titers reached a laboratory-specific "critical" level indicative of high risk of fetal anemia, ($\geq$1:64 for anti-RhD and most other antibodies and $\geq$1:8 for anti-Kell) [19,26], the detection of fetal anemia in cases of red cell alloimmunization associated with hemolysis was based on spectrophotometric measurement of the amniotic fluid for increased bilirubin concentration. Bilirubin level was expressed as the change in optical density (OD) at a wavelength of 450 nm ($\mathbf{\Delta}$ OD450). These values were plotted on Liley's curve or Queenan's curve (<27 weeks) to predict fetal anemia [27]. The use of Δ OD450 to screen for fetal anemia has now been abandoned, given the availability of noninvasive and more accurate alternatives; MCA-PSV testing has replaced serial invasive testing after the demonstration that Doppler assessment of the MCA-PSV has higher sensitivity and accuracy for the prediction of severe fetal anemia than amniotic-fluid $\mathbf{\Delta}$ OD450 in Rh-alloimmunized pregnancies [28]. Once critical titers of causative antibodies are reached, MCA-PSV is assessed to determine the optimal timing of FBS.

Parvovirus B19 (PB19)

Diagnosis of maternal infection relies on the detection of PB19-specific immunoglobulin (Ig) M and/or IgG antibodies. Viremia develops approximately 1 week after inoculation. IgM is detectable 7–10 days after infection, peaks at 10–14 days, and remains detectable for up to 6 months. Two weeks after infection, IgG becomes detectable and confers lifelong immunity. Fetal infection is confirmed by polymerase chain reaction for PB19 DNA in the amniotic fluid or fetal blood. Nonimmune fetal hydrops typically develops 2–6 weeks after seroconversion but may occur up to 10–12 weeks later. Ultrasound and MCA-PSV measurements should be performed every 1–2 weeks for approximately 10–12 weeks from maternal seroconversion, with referral to a fetal medicine unit for treatment if there is evidence of fetal anemia or hydrops [10].

Twin anemia–polycythemia sequence (TAPS)

The antenatal diagnosis of TAPS, which is a complication peculiar of monochorionic twin pregnancy, depends on Doppler ultrasound abnormalities and is based on increased MCA-PSV of >1.5 multiples

MoM, predicting anemia in the donor, and reduced MCA-PSV of <1.0 MoM in the recipient, a sign of polycythemia [29]. Absence of oligo-polyhydramnios is a conditio sine qua non because its presence is pathognomonic for TTTS. Recently, it has been proposed to use a Δ MCA-PSV > 0.5 MoM between the two twins as a more accurate predictor of TAPS [30].

Fetomaternal hemorrhage (FMH)

Prenatal diagnosis of severe FMH is difficult. A decreased perception of fetal movements and abnormal cardiotocography are usually present but often not specific. A sinusoidal cardiotocogram, which carries a strong but not exclusive correlation with fetal anemia, might be found in approximately two thirds of the cases, while in the remaining nonreactive tracings, decelerations or tachycardia has been described [31]. In most countries, pregnant patients are recommended to report rapidly decreased perception of fetal movements because this is associated with an increased risk of adverse outcome. However, there is no consensus on which test to perform in these cases. Usually, the first approach is cardiotocography and ultrasound evaluation of fetal size, movements, umbilical artery Doppler, and amniotic fluid volume. A similar diagnostic workup is recommended after maternal trauma. Severe FMH may occur in both circumstances; therefore, in such cases, MCA-PSV should be assessed, as this may rapidly provide a major clue to the diagnosis of fetal anemia [31]. The Kleihauer, Braun and Betke stain test or flow cytometry can then be used for FMH diagnosis and quantification. Whether to expedite delivery or perform an IUT will depend on GA, antenatal test results, and availability of expertise [10].

Alpha (α)-thalassemia

Alpha (α)-thalassemia is caused by the defective synthesis of α-globin chains and is the most common cause of nonimmune fetal hydrops in Southeast Asia. The α-globin gene cluster consists of four copies of the α-globin gene ($\alpha\alpha/\alpha\alpha$). α-Thalassemia can be classified into four types according to the number of functional α-globin genes: silent carrier state (-$\alpha/\alpha\alpha$), α-thalassemia trait ($-/\alpha\alpha$ (cis) or -α/-α (trans)), Hb H disease (-−/$-\alpha$), and α-thalassemia major ($-/-$) (Hb Bart's or homozygous α-thalassemia). If both parents carry the cis deletion ($-/\alpha\alpha$), the inheritance risk for α-thalassemia major is 25%. Fetuses with homozygous α-thalassemia cannot produce normal fetal Hb ($\alpha 2\gamma 2$) and produce Hb Bart's ($\gamma 4$) instead. Given the severe impairment in tissue oxygen delivery, the sequelae of fetal anemia and hydrops may occur at higher Hb values than those seen with RBC alloimmunization, making MCA-PSV Doppler less predictive of disease severity. Prenatal diagnosis is established by DNA analysis by chorionic villus sampling performed after 10 gestational weeks or amniocentesis after 15 weeks. Serial sonographic evaluation for cardiomegaly and placental thickness can be used as a screening tool in early pregnancy. When the predictive values of cardiothoracic ratio (CTR), MCA-PSV, and placental thickness were compared, CTR was found to be superior, and sensitivity at 12–15 weeks was further increased by addition of MCA-PSV measurement [10,32]. Historically, fetal α-thalassemia major was considered to be a uniformly lethal condition, but with the advent of intrauterine transfusions, increasing numbers of live births have been reported; however, in the absence of curative therapy, prenatal treatment raises ethical dilemmas and requires detailed counseling from a multidisciplinary team.

Intrauterine transfusion

Technique

Intravascular intrauterine transfusion (IUT) is currently the most common and established technique for the treatment of fetal anemia and can be employed for almost all the etiologies listed in the previous section [33]. IUT is indicated only in the case of moderate or severe anemia, but the definition of the latter may vary between different fetal medicine centers (e.g., Hb concentration 4–5 SDs below

mean for GA, Hb deficit >5 g/dL, absolute Hb concentration <10 g/L, or hematocrit <30 [6,10]). IUT is usually performed with fresh donor red blood cells, 0-negative, CMV-negative, washed, irradiated, leukocyte depleted, and packed to a hematocrit of 75–80%. The blood is negative for the antigens against which the mother is eventually immunized and often is checked for other antigens (e.g., Duffy, Kidd, and S blood groups) against which she may develop antibodies.

IUT is performed under aseptic conditions, with continuous ultrasound guidance, using a 20–22 gauge needle. The umbilical vein is targeted at the placental cord insertion in its intrahepatic course [34] or in a free loop of cord. The fetal liver and placental cord insertion are considered the safest sites, while puncture of a free loop seems to have a higher complication rate [6,10]. Arterial puncture should also be avoided because of the risk of arterial spasm. Fetal paralysis with atracurium, vecuronium, or rocuronium should be considered, and the drug can be delivered either intramuscularly or directly into the umbilical vein [6,7,10]. Fetal paralysis reduces the risk of needle displacement with fetal movements and may decrease associated complications such as arterial spasm, cord hematoma, or excessive bleeding from tearing of the puncture site; it may be particularly useful when the procedure is performed at advanced GAs or is expected to be prolonged; the routine use of fetal paralysis was associated with better outcomes in a recent large series of 1678 IUTs [35]. Fetal sedation with fentanyl is not routinely advocated [6].

Once the umbilical vein is accessed, a fetal blood sample is obtained and sent to the laboratory for a fetal blood count and eventually additional tests (see Table 2). Hb/hematocrit assessment can also be obtained with point-of-care analyzers. If blood flow though the needle is not immediate, the tip of the needle may be in Wharton's jelly; the needle can slowly and carefully be repositioned to enter into the vein. If in doubt about the needle position, some operators document blood flow in the umbilical vein by flushing a small amount of saline; in this case, the first mL of blood drawn should be discarded before any testing due to possible dilution [7].

The target fetal hematocrit should be approximately 40%–50%, although some suggest an increase to 25% only in case of severe anemia before 24 weeks, eventually followed by a second transfusion after 48 h [7]. The volume of blood to be transfused depends on donor and fetal pretransfusion and target Hb/hematocrit. Table 3 shows Rodeck's formula and the simplified formula by Giannina et al. (which assumes a donor hematocrit of 75%). Both were shown to be equivalent in clinical use. Moreover, when transfusing large volumes of blood, it is common practice to obtain a sample during the second half of the transfusion to avoid unnecessary overload [6,7,10].

Table 2
Investigations for fetal anemia. Reproduced, with permission, from Abbasi [10].

Maternal
Detailed family and pregnancy history (e.g., ethnicity, consanguinity, genetic syndromes, infection exposure, and trauma), CBC, blood group, and screen (indirect Coombs titer if antibody screen +)
Kleihauer–Betke, flow cytometry
Hemoglobin electrophoresis
Serology (PB19 IgG and IgM, CMV IgG and IgM (avidity testing if IgM+), toxoplasmosis IgG and IgM, syphilis testing)
Referral to fetal medicine unit with detailed fetal and placental ultrasound and MCA-PSV Doppler with or without fetal echocardiogram if hydrops
Fetal
Fetal blood sample (FBS)[a] should be sent for blood type, CBC, Hb/Hct, platelet count, direct Coombs, reticulocyte count and total bilirubin, and PCR for CMV and PB19 with or without syphilis and toxoplasmosis
Nonstress test for sinusoidal fetal heart rate
Rare causes of fetal anemia
Hematology and genetics consultation
Parental hemoglobin, high-performance liquid chromatography, and RBC enzyme assays (i.e., pyruvate kinase and G6PD).
Fetal peripheral smear, hemoglobin electrophoresis and chromosome fragility studies (i.e., Fanconi anemia)
If elevated white blood cell count, obtain differential and peripheral smear and consider congenital leukemia or transient myeloproliferative disorder

[a] FBS should be considered if sonographic features suggest fetal anemia. CBC, complete blood count; CMV, cytomegalovirus; G6PD, glucose-6 phosphate dehydrogenase; Hb, hemoglobin; Hct, hematocrit; Ig, immunoglobulin; MCA-PSV, middle cerebral artery peak systolic velocity; PCR, polymerase chain reaction; PB19, parvovirus B19; RBC, red blood cell.

Table 3
Formulas for calculating the volume of transfusion.

Rodeck et al. [65] Intravascular transfusion volume (mL) $= \frac{(target\ Hb - fetal\ Hb) \times fetoplacental\ blood\ volume_a}{(donor\ Hb - target\ Hb)}$ The fetoplacental blood volume is estimated by one of the following: • 0.1 mL/g of estimated fetal weight [66] • 1.046 + (fetal weight in g) × 0.14 [67] • 0.15 mL/g of estimated fetal weight [68]
Giannina et al. [66] Intravascular transfusion volume (mL) = 0.02 × target increase in fetal Ht per 10% × g of estimated fetal weight[b]
Intraperitoneal transfusion [7] Intraperitoneal transfusion volume (mL) = (gestational age in weeks − 20) × 10

Hb: hemoglobin concentration; Ht: hematocrit.
[a] Can also be used for hematocrit.
[b] Can only be used for hematocrit; assumes donor hematocrit of 75%.

Repeat transfusions

The use of MCA-PSV to predict fetal anemia becomes less reliable after several intrauterine transfusions, with false-positive rates of 14%, 37%, and 90% for the detection of 95% of severely anemic fetuses following the first, second, and third intrauterine transfusions, respectively [36]. In anemic fetuses, the increase in MCA-PSV reflects a hyperdynamic circulation because of decreased blood viscosity; following intrauterine transfusion with adult blood cells, which have a lower viscosity, the use of MCA-PSV to predict fetal anemia becomes less reliable [36]. For the same reasons, false-positive results are also more frequent at 34–37 weeks in the case of previous intrauterine transfusion [24]. Generally, the timing of subsequent intrauterine transfusions may be based on the anticipated decline in fetal Hb (for example, using 0.4 g/L/day, 0.3 g/L/day, and 0.2 g/L/day Hb decline for the first, second, and third intrauterine transfusion intervals, respectively, or a decline of 1%/day in fetal hematocrit [10,36]), as well as on MCA-PSV measurements [37]. A randomized controlled trial based on 71 women compared the two strategies (timing of repeat transfusion based on MCA-PSV >1.5 MoM vs. estimated fall in fetal hematocrit 1%/day or Hb 0.3 g/L/day) and found no significant differences in mean Hb levels at birth or in the number of IUTs performed after randomization [38].

Delivery

There is no high-quality evidence on when to deliver a fetus who has received IUTs. The ideal result is to deliver at or near to term a neonate with no or moderate anemia, not needing exchange transfusions or prolonged phototherapy. In a pregnancy complicated by maternal alloimmunization, with a stable fetus who has received serial IUTs, most clinicians would consider a last transfusion not later than 34–35 weeks, aiming to deliver the baby at 37–38 weeks [6,7,10].

Complications and short-term outcome

A number of complications can affect IUT, namely, rupture of membranes, infection, bleeding from the puncture site, cord hematoma leading to vessel compression, bradycardia, or tachycardia [6]. Some of these complications may require the emergency delivery of a viable fetus. For these reasons, steroid administration should be considered if the pregnancy is viable, and the procedure should be performed in a setting allowing an emergency cesarean delivery [7]. Recently, Zwiers et al. reviewed the complication rates of IUT in cohort studies published in the last ten years: they observed a complication rate of 7.8% per fetus and 2.7% per procedure; the procedure-related fetal loss rate was 2.1% per fetus and 0.7% per procedure; overall, the live birth rate was 95.5% [6]. The same authors reported their institutional series of 1678 IUT procedures [35]: Perinatal survival increased from 88.6% in 1988–2000 to 97.0% in 2001–2015; in the same time intervals, the procedure-related fetal loss rate declined from 4.7% to 1.8% per fetus and from 1.6% to 0.6% per procedure. They identified arterial puncture, needling of

a free loop of cord, and not using fetal paralysis as risk factors for complications [35,39]. During the same time period, the average severity of the treated cases improved, with a smaller proportion of hydropic fetuses [35,40]; this explains in part the overall improvement in survival but not the reduction in procedure-related complications, the latter being probably attributable to refinements in technique and operator experience. Severe anemia is a risk factor for acquired brain lesions, and an increased attention to fetal brain assessment at follow-up scans is necessary [41,42]; some authors suggest a low threshold for fetal brain MRI in such cases [43].

Despite intrauterine treatment, newborns affected with HDFN still have a significant chance of delivering before 35 weeks (approximately 1 in 5), and the majority of them will need exchange transfusion to prevent kernicterus [44,45]. Newborns who had multiple transfusions will often have suppressed reticulocytes and may need top-up transfusions until hematopoiesis resumes [7].

Special considerations

Although IPT is no longer considered the first choice for the treatment of fetal anemia, this technique may still have a role in early pregnancy (before 22 weeks), when the fetal loss rate of IUT seems to be higher [10,46,47]. Moreover, fetuses with severe anemia at early gestation and those with hydrops are considered to be at increased risk of complications from IUTs, which might be explained by volume overload with transfusion. A possible approach to these cases is to perform an IPT (formula to calculate volume given in Table 3) or to combine IPT with IUT, transfusing approximately two thirds of the total volume intravascularly, and one third intraperitoneally. RBCs are slowly absorbed from the peritoneal cavity, and the combined approach might even reduce the Hb drop rate between procedures, allowing less frequent intervals between transfusions [6,48].

Intrauterine exchange transfusion is another approach that might help reduce volume overload, obtain a more stable hematocrit, and increase the interval between transfusions. With this technique, small volumes of blood of the anemic fetus are slowly withdrawn and replaced with the same volume of packed red blood cells [49]. The procedure seems to be safe in experienced hands [50], but it does not seem to provide significant improvements compared to “simple” IUT [51]. Partial exchange transfusion, with the goal of reducing hematocrit, has been proposed for the recipient polycythemic twin in TAPS, combined with standard IUT in the anemic donor twin [52]; however, clinical data regarding this approach to monochorionic twin pregnancies complicated with TAPS are limited [53,54].

Intravenous immunoglobulin therapy

There is a case for the use of intravenous immunoglobulin (IVIG) therapy in HDFN, as Ig saturate the Fc-mediated transplacental transport of IgGs, downregulate maternal Ig production, and may decrease the macrophagic uptake of opsonized RBCs in the fetus [6]. IVIG might decrease hemolysis but do not treat fetal anemia [55]; hence, their possible role is in avoiding or delaying anemia in pregnancies at high risk of HDFN. The limited evidence of IVIG (summarized in Ref. [6]) suggests that IVIG treatment, alone or in combination with therapeutic plasma exchange, might reduce the risk of hydrops and fetal death in severely Rh-sensitized patients. Similar findings were observed in a recent multicenter cohort including 52 patients [56]. However, better evidence is needed before the widespread use of IVIG treatment, which is expensive and not without complications.

Long-term outcome

As severe anemia and hydrops for a prolonged period can lead to ischemic and/or hemorrhagic brain lesions and consequent neurodevelopmental impairment, long-term follow-up assessments are needed to establish neurodevelopmental outcome in these children. Lindenburg et al. studied 291 children at a median age of 8.2 years (LOTUS study): cerebral palsy was present in 6 (2.1%) children, severe developmental delay in 9 (3.1%) children, and bilateral deafness in 3 (1%) children. Overall, the incidence of neurodevelopmental impairment was 4.8% (14/291) and severe hydrops, number of IUT, and severe neonatal morbidity were found to be risk factors for an adverse neurological outcome [44]. At the same center, a study on health-related quality of life and behavioral functioning compared the score results of

the questionnaires of 285 children and adolescents treated with IUT for alloimmune anemia with Dutch norm data. Overall, the results were generally good; lower scores of cognitive functioning in children between 6 and 11 years of age were reported by parents, whereas behavioral difficulties were reported in 15% of children and they were significantly associated with maternal education [57].

Fetal anemia due to PB19 infection and treated with intrauterine transfusion seems to be associated with less favorable survival rates ranging from 67% to 85% [58–61]. Severe anemia (diagnosed sometimes later compared to those cases with alloimmunized pregnancies) and the neurotropic nature of this virus infecting nerve cells may both lead to cerebral injury in fetuses infected in utero. Limited data are available on their long-term neurodevelopmental outcome, and the largest study considered only 28 patients; all cases described in the literature were hydropic, and major neurodevelopmental impairment has been reported in up to 12.5% of children [58–61].

Few studies have focused on long-term cardiovascular consequences in children born with red cell alloimmunization. Theoretically, the chronic anemia may increase the cardiac output and induce myocardial hypertrophy; only one study evaluated by echocardiography the cardiac structure and function in 25 children treated with intrauterine transfusion for anemia due to red cell alloimmunization and found a significantly smaller ventricular mass than that in the control group [62].

Recently, Wallace et al. evaluated cardiovascular disease risk factors in 95 adults treated with intrauterine transfusion in utero for severe anemia due to Rhesus disease in comparison to nonanemic siblings in a retrospective cohort study; the exposed participants had smaller left ventricular volumes, increased left ventricular wall thickness, and reduced myocardial perfusion at rest, and the authors concluded that severe anemia in utero could increase the cardiovascular disease risk in adulthood [63].

PB19 infection is also known to be a possible cause of myocarditis in children [64]. There are no published data on the cardiovascular follow-up of survivors with PB19 infection in utero, but the severe fetal anemia associated with a possible viral myocarditis could lead to potential long-term sequelae.

Further studies with international collaborations due to the relative rarity of the cases diagnosed and treated in utero are needed to better understand the possible mechanisms of damage and long-term sequelae in fetuses born after intrauterine transfusion for severe anemia.

Summary

Fetal anemia is the earliest and most successful example of fetal therapy. It has been known for many years as a dangerous complication of pregnancy. Despite the high risk of intrauterine death and severe complications, survival rates as high as 95% have been reported in recent series [6]. The most common causes are maternal alloimmunization and parvovirus B19 infection, although it can be associated with many different pathological conditions that should be considered when a differential diagnosis is needed. Earlier recognition by Doppler ultrasonographic assessment of the MCA-PSV and refinements in IUT techniques have contributed to improved outcomes. However, there are still significant knowledge gaps; the additional role of intravenous Ig therapy and the long-term consequences of fetal anemia need further research.

Conflict of interest

The authors have no conflict of interest to declare.

Practice points

- A standardized technique should be used for the Doppler ultrasonographic assessment of the peak velocity of systolic blood flow in the middle cerebral artery.
- IUT is better performed targeting the umbilical vein at the placental cord insertion or in its intrahepatic course.
- The volume of blood transfused must be calculated considering pretransfusion Hb concentration or hematocrit, donor and target levels, and fetoplacental blood volume.

Research agenda

- Randomized trials evaluating the role of intravenous Ig therapy.
- Controlled studies on the management of early severe anemia.
- Controlled studies on the long-term outcomes of fetal anemia.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2019.01.001.

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