Fetal anemia

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Introduction

Fetal anemia is a relatively rare but serious condition. An immune-related cause is most common, involving red-blood-cell (RBC) alloimmunization, followed by non-immune causes, such as parvovirus B19 infection and, more rarely, hemoglobinopathies, fetomaternal hemorrhage (FMH) and monochorionic twin complications, among others. Several advances have been made in the diagnosis and treatment of fetal anemia. High-resolution ultrasound now permits accurate, non-invasive screening techniques and associated risks and benefits, as well as short- and long-term outcomes following IUT.

Definition of fetal anemia (Table 1)

As fetal hemoglobin (Hb) values increase gradually during pregnancy, anemia may be classified based on the degree of Hb deviation from the mean for gestational age (GA)5 or on multiples of the median (MoM)1 for GA (Table 1). Hydrops typically does not develop until the Hb deficit is > 70 g/L or 70 g/L.5

Etiology of fetal anemia (Table 2)

Red-blood-cell (RBC) alloimmunization/hemolytic disease of the fetus and newborn (HDFN)

Alloimmunization occurs following maternal exposure to paternally derived RBC antigens on fetal cells, resulting in maternal antibody formation and secondary fetal RBC hemolysis, anemia, hydrops and, ultimately, fetal demise1. Although over 50 RBC antigens have been associated with fetal hemolysis, severe fetal anemia results most commonly from Rhesus (Rh) D, Rhc or Kell alloimmunization7.

RBC alloimmunization is the leading cause of fetal anemia, despite standardized protocols for RhD immune globulin (RhIG) 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 age1.

Pregnancies at risk are identified on the basis of a previous history of hemolytic disease of the fetus and newborn (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. Traditionally, fetal genotyping was determined by amniocentesis, with a sensitivity of 98.7% and specificity of 100% for RhD status8. The discovery of cell-free DNA in the maternal plasma has since enabled non-invasive determination of the fetal RhD genotype9. Experience with this approach is extensive, with prediction accuracy and test sensitivity approaching 100%, and very few false-negative results7. While results can be obtained as early as 10 gestational weeks, 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’ gestation.

In sensitized pregnancies, serial titers are performed, typically every 4 weeks until 28 weeks’ gestation and every 2 weeks thereafter7. Historically, once titers reached a laboratory-specific ‘critical’ level indicative of high risk of fetal anemia, commonly defined as 1:16 for anti-RhD and most other antibodies and 1:8 for anti-Kell10, serial amniocenteses were then performed for bilirubin levels to estimate the severity of hemolysis. Spectrophotometry was used to quantify bilirubin level, which was expressed as the change in optical density (OD) at a wavelength of 450 nm (ΔOD450). These values were plotted on Liley’s curve11 or Queenan’s curve (<27 weeks)12 to predict fetal anemia. MCA-PSV testing has now replaced serial invasive testing after a randomized control trial demonstrated that Doppler assessment of the MCA-PSV had higher sensitivity and accuracy for prediction of severe fetal anemia compared with amniotic-fluid ΔOD450 in Rh-alloimmunized pregnancies2. Once critical titers are reached, MCA-PSVs are measured weekly to determine optimal timing of FBS.
### Table 1 Definitions of fetal anemia

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<thead>
<tr>
<th>Definition</th>
<th>Reference</th>
<th>Severity</th>
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<tbody>
<tr>
<td>Hemoglobin deviation from GA mean</td>
<td>Nicolaides et al.¹⁵</td>
<td>Mild: &lt; 20 g/L</td>
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<tr>
<td>Hemoglobin values expressed as MoM</td>
<td>Mari et al.¹; Goodwin and Breen¹⁶</td>
<td>Moderate: 20 – 70 g/L</td>
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<tr>
<td>Hematocrit</td>
<td>Moise Jr and Argoti¹⁰</td>
<td>Severe: &gt; 70 g/L</td>
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GA, gestational age; MoM, multiples of the median.

### Table 2 Etiology of fetal anemia

### Classification Causes

**Immune**
- RBC alloimmunization
  - Rh blood group (D, c, C, E, Kell, Duffy, Kidd (Jk⁺, Jk⁻)) or any IgM RBC antibody

**Non-immune**
- Congenital infections
  - Parvovirus B19, CMV, toxoplasmosis, syphilis
  - Hemoglobinopathies (e.g. α-thalassemia major), RBC membrane or enzyme disorders (e.g. G6PD deficiency, pyruvate kinase deficiency)
  - Fanconi anemia, Diamond–Blackfan anemia
  - Congenital leukemia, transient myeloproliferative disorder
  - Sacrococcygeal teratoma, liver hemangioma, hepatoblastoma, diffuse neonatal hemangiomatisos, placental chorangioma, fetal or placental arteriovenous malformations, placental mesenchymal dysplasia

**Bone-marrow disorders**
- Fanconi anemia, Diamond–Blackfan anemia
- Congenital leukemia, transient myeloproliferative disorder
- Sacrococcygeal teratoma, liver hemangioma, hepatoblastoma, diffuse neonatal hemangiomatisos, placental chorangioma, fetal or placental arteriovenous malformations, placental mesenchymal dysplasia
- Placental abruption, trauma
- Lysosomal storage disorders (e.g. Niemann–Pick, Gaucher disease, mucopolysaccharidosis), neonatal hemochromatosis

**Fetomaternal hemorrhage**
- Placental abruption, trauma
- Lysosomal storage disorders (e.g. Niemann–Pick, Gaucher disease, mucopolysaccharidosis), neonatal hemochromatosis

**Rare genetic disorders**
- Lysosomal storage disorders (e.g. Niemann–Pick, Gaucher disease, mucopolysaccharidosis), neonatal hemochromatosis

**Complications of monochorionic placentation**
- TAPS, twin anemia–polycythemia sequence

*Potential candidates for intrauterine transfusion (IUT).* CMV, cytomegalovirus; G6PD, glucose-6 phosphate dehydrogenase; IgM, immunoglobulin; RBC, red blood cell; Rh, Rhesus; TAPS, twin anemia–polycythemia sequence.

**Parvovirus B19 (PB19) and other congenital infections**

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; less commonly, it is transplacental or from blood products. The overall risk of vertical transmission is approximately 17–33%, with the highest risk occurring prior to the third trimester.

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. *Erythema infectiosum*, or 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. Rare presentations include myocarditis and heart failure, aplastic crisis in the setting of chronic anemia, and persistent infection and anemia in immunocompromised individuals.

Fetal infections are mostly asymptomatic without sequelae, but may result in miscarriage, severe anemia and non-immune hydrops (NIH) and stillbirth. Marked fetal ascites is pathognomonic of PB19 infection (Figure 1). 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 will develop hydrops.

Diagnosis of maternal infection relies on 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 amniotic fluid or fetal blood. NIH typically develops...
2–6 weeks after seroconversion\textsuperscript{19} but may occur up to 10–12 weeks later\textsuperscript{20}. Ultrasound and MCA-PSV measurements should be performed every 1–2 weeks for approximately 10–12 weeks from maternal seroconversion\textsuperscript{14}, with referral to a fetal medicine unit for FBS with or without IUT if there is evidence of fetal anemia or hydrops.

Rarely, fetal anemia and hydrops can be caused by other congenital infections, including cytomegalovirus (CMV)\textsuperscript{21}, syphilis\textsuperscript{22} and toxoplasmosis\textsuperscript{23}. Other ultrasonographic features of congenital infections may include ascites, placentomegaly, hepatosplenomegaly, echogenic bowel, liver or intracranial calcifications, ventriculomegaly and intrauterine growth restriction (IUGR).

### Hemoglobinopathies, hemolytic anemias and bone-marrow-failure syndromes

Alpha (α)-thalassemia is caused by the defective synthesis of α-globin chains and is the most common cause of NIH in Southeast Asia. The α-globin gene cluster consists of four copies of the α-globin gene (αα/αα). α-thalassemia can be classified into four types based on the number of functional α-globin genes: silent carrier state (−/−αα), α-thalassemia trait (−/αα cis or α/−αα trans), α-thalassemia disease (−/−α) and α-thalassemia major (−/−−) (Hb Bart’s or homozygous α-thalassemia). If both parents carry the cis deletion (−/−αα), the inheritance risk for α-thalassemia major is 25%. Fetuses with homozygous α-thalassemia cannot produce normal fetal Hb (ααγγ), instead producing Hb Bart’s (γγ). Clinical features include: cardiomegaly, ascites, hydrops, IUGR, limb defects\textsuperscript{24}, intrauterine fetal death (IUD) and neonatal death (NND)\textsuperscript{25–27}. Given the severe impairment in tissue oxygen delivery, the sequelae of fetal anemia and hydrops may occur at higher Hb values than seen with RBC alloimmunization, making MCA-PSV Doppler less predictive of disease severity. Maternal complications may include ‘mirror’ syndrome and antepartum hemorrhage\textsuperscript{25}.

Prenatal diagnosis is established by DNA analysis via chorionic villus sampling performed after 10 gestational weeks or amniocentesis after 15 weeks. Alternatively, serial sonographic evaluation for cardiomegaly and placentomegaly can be used as a screening tool in early pregnancy. The sensitivity and specificity of placentomegaly for detection of α-thalassemia major were 72% and 97%, respectively, before 12 weeks and 95% and 97%, respectively, after 12 weeks\textsuperscript{28}. Using a cardiothoracic ratio (CTR) ≥ 0.5 to estimate cardiomegaly, sensitivity and specificity were 100% at 12–13 weeks\textsuperscript{26}. When the predictive value of CTR, MCA-PSV and placentomegaly were compared, CTR was found to be superior, and sensitivity at 12–13 weeks was further increased by addition of MCA-PSV measurement\textsuperscript{27}.

Historically, fetal α-thalassemia major was considered to be a uniformly lethal condition, but, with the advent of IUT, increasing numbers of live births have been reported\textsuperscript{29}. However, in the absence of curative therapy, prenatal treatment raises ethical dilemmas and requires detailed counseling from a multidisciplinary team.

### Congenital leukemia and myeloproliferative disorders

Congenital leukemia and occasionally transient myeloproliferative disorder may present prenatally with fetal anemia, hepatosplenomegaly, polyhydramnios, placentomegaly, hydrops and IUFD\textsuperscript{29}, most commonly associated with trisomy 21\textsuperscript{29,30}.

### Placental/fetal tumors

Placental chorangiomas are the most common benign placental tumor and can be associated with fetal anemia\textsuperscript{31,32}, secondary to fetal hemorrhage\textsuperscript{31} or consumption and destruction of fetal RBCs within the narrow, thrombosed vasculature of the chorangioma\textsuperscript{33}. Other complications include NIH, polyhydramnios, preterm labor, IUGR and pre-eclampsia, particularly if tumors are > 4 cm\textsuperscript{32}. Fetal sacrococygeal tumors can also result in fetal anemia, due to hemorrhage within the tumor and RBC consumption, with secondary high-output cardiac failure and NIH\textsuperscript{34}.

### Fetomaternal hemorrhage (FMH)

Traditionally, FMH has been defined as hemorrhage of ≥ 30 mL fetal blood into the maternal circulation, as this is the volume of Rh-positive whole fetal blood that is covered by a standard 300-μg dose of RhIG to prevent alloimmunization\textsuperscript{35}. Large or massive FMH has been defined as blood loss of 80–150 mL\textsuperscript{36} or > 20 mL/kg\textsuperscript{37}, however, there is no fixed volume above which fetal morbidity or mortality will result unequivocally. Although the majority of FMHs remain unexplained\textsuperscript{35}, risk factors include: external cephalic version\textsuperscript{38}, abdominal trauma\textsuperscript{39}, placental abruption, placenta previa, IUFD, Cesarean section, manual removal of the placenta and amniocentesis\textsuperscript{35}.

Massive FMH with fetal hydrops at 26–28 weeks has been managed with serial IUTs; however, outcomes are variable, ranging from resolution of hydrops and live birth\textsuperscript{40} to IUFD\textsuperscript{41}. Whether to expedite delivery or perform an IUT will depend on GA, antenatal test results and availability of expertise.

### Monochorionic complications: twin–twin transfusion syndrome (TTTS), twin anemia–polycythemia sequence (TAPS) and cotwin demise

Twin–twin transfusion syndrome (TTTS) and twin anemia–polycythemia sequence (TAPS) are chronic forms of fetofetal transfusion\textsuperscript{42}. TTTS complicates up to 15% of monochorionic diamniotic (MCDA) twin pregnancies and pathogenesis is related to unbalanced blood flow through placental vascular anastomoses\textsuperscript{43}. A gradual blood-flow shift develops, resulting in oliguric oligohydramnios in the donor and polyuric polyhydramnios and volume overload in the recipient\textsuperscript{43}, potentially leading to hydrops secondary to right ventricular dysfunction\textsuperscript{44}. A large intertwin hemoglobin difference is not generally seen, unless there is coexisting TAPS.

TAPS is characterized by a Hb discordance in MCDA twins in the absence of the oligopolyhydramnios sequence
seen with TTTS, and occurs when there are only a few, tiny (< 1 mm), unidirectional arteriovenous vascular anastomoses, with sparse or absent compensatory arterioarterial anastomoses. TAPS may occur spontaneously in 3–5% of MCDA twins, usually presenting after 26 weeks’ gestation (Figure 2), or in 2–13% of TTTS cases, following incomplete laser ablation of placental anastomoses.

Cotwin demise may result in an acute hemodynamic imbalance, due to a massive transfer of blood from the survivor to the dead twin via the placental anastomoses in monochorionic placenta, causing anemia, neurological handicap or death of the remaining twin. Although IUT can correct the anemia, whether or not it impacts on neonatal or neurodevelopmental outcome is unknown.

Investigation of suspected fetal anemia (Table 3)

Recommended investigations for evaluation of suspected fetal anemia are listed in Table 3. Referral to a maternal fetal medicine specialist and a tertiary care center with expertise in FBS and IUT is indicated.

Ultrasonographic assessment of fetal anemia (Table 4)

The first manifestation of hydrops secondary to fetal anemia is always ascites, followed by placental thickening and hepatomegaly; associated pleural or pericardial effusions are rare. Fetal liver length > 90th percentile, splenomegaly (spleen perimeter > 2SD) and Doppler measurements of mean blood velocity in the fetal aorta and splenic artery PSV were also found to correlate with fetal anemia. When Oepkes et al. compared fetal liver length, spleen perimeter, umbilical vein (UV) diameter, placental thickness and UV and aortic flow velocities, only Doppler parameters were predictive of severe anemia in non-hydropic fetuses.

Middle cerebral artery (MCA) Doppler studies and prediction of fetal anemia. Initial studies in fetal lambs, measuring blood flow in relation to hematocrit (Hct), demonstrated compensatory increased flow to the brain, heart and adrenals to maintain stable oxygen delivery across a range of Hct; this was also replicated in humans. An inverse relationship was also noted between fetal Hct and MCA-PSV. Subsequently, Mari et al. demonstrated that MCA-PSV > 1.50 MoM in non-hydropic fetuses at risk of RBC alloimmunization could detect all cases of moderate to severe anemia, with a false-positive rate of 12%. Oepkes et al. thereafter confirmed the superioriy of MCA-PSV over amniotic-fluid ΔOD₄₅₀, making serial amniocenteses for fetal anemia screening essentially obsolete.

Obtaining MCA-PSV measurements: technical aspects. 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 closest to the probe 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°, and always < 30° (Figure 3). Higher inter- and intraobserver variability results from angle correction and sampling of more distal regions of the MCA. The fetus should be quiescent, as heart-rate accelerations and movement can alter measurements. Other factors that may influence MCA-PSV include: gender, cardiac status, uterine contractions, fetal behavioral state, advanced GA and previous IUTs. Elevated MCA-PSVs may also be seen in abnormal placentation and IUGR, reflecting cerebral autoregulation in response to hypoxemia and hypercapnia. These factors, in addition to insufficient...
Table 3 Investigation of fetal anemia

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<thead>
<tr>
<th>Maternal</th>
<th>Detailed family and pregnancy history (e.g. ethnicity, consanguinity, genetic syndromes, infection exposure and trauma)</th>
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<tr>
<td></td>
<td>CBC, blood group and screen (indirect Coombs titer if antibody screen +)</td>
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<td></td>
<td>Kiehauer–Betke, flow cytometry</td>
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<td></td>
<td>Hemoglobin electrophoresis</td>
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<td></td>
<td>Serologies (PB19 IgG and IgM, CMV IgG and IgM (avidity testing if IgM +), toxoplasmosis IgG and IgM, syphilis testing)</td>
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<td>Referral to fetal medicine unit with detailed fetal and placental ultrasound and MCA-PSV Doppler with or without fetal echocardiogram if hydrops</td>
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**Fetal**

Fetal blood sample (FBS) should be sent for blood type, CBC, Hb/Hct, platelet count, direct Coombs, reticulocyte count and total bilirubin, PCR for CMV and PB19 with or without syphilis and toxoplasmosis.

Non-stress 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, 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

*FBS should be considered if sonographic features suggest fetal anemia (see text). 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 4 Sonographic features of fetal anemia

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<th>Sonographic features</th>
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<td>General</td>
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<td>Specific clinical conditions</td>
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<td>α-thalassemia major</td>
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<tr>
<td>Congenital infections</td>
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<tr>
<td>Complications of MC twins</td>
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<tr>
<td>TAPS</td>
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CTR, cardiothoracic ratio; GA, gestational age; MC, monochorionic; MCA-PSV, middle cerebral artery peak systolic velocity; TAPS, twin anemia–polycythemia sequence.

Attention to proper technique, may in part explain the false-positive rate of MCA-PSV for prediction of fetal anemia, described by Mari et al.¹.

**Fetal blood sampling (FBS)⁶²,⁶³**

We perform FBS only when the MCA-PSV is above 1.5 MoM and trending upwards. Investigations at the time of FBS are listed in Table 3. Rare causes of anemia should be evaluated in conjunction with a hematologist. Administration of corticosteroids for fetal lung maturity should be considered prior to FBS after viability.

**Treatment: intrauterine transfusion (IUT)**

The goal of IUT in HDFN is to replace the fetal blood with Rh-negative donor blood, thus suppressing fetal erythropoiesis. IUT is generally indicated for fetal Hct < 30%¹⁰ or Hb < 10 g/L⁶⁴. Fresh, CMV-negative, leukoreduced, irradiated, Type-O, RhD-negative donor RBCs, cross-matched to a maternal sample and packed with

Figure 3 Axial section of fetal brain with color flow mapping showing circle of Willis (**) with Doppler gate placed within proximal third of middle cerebral artery (MCA) to measure peak systolic velocity (in cm/s).
to a Hct of 75–80%, are used. Autologous washed maternal blood can also be used for IUT once the maternal Hb level is > 120 g/L, which eliminates the risk of sensitization to new RBC antigens in random donor blood. Platelets should be available if PB19 or CMV are suspected, or in the presence of hydrops or hepatosplenomegaly. Coexistent severe thrombocytopenia has been reported in hydropic alloimmunized pregnancies and hydropic fetuses with PB19.

When a previous pregnancy has been complicated by HDFN, titers are less reliable predictors of severe fetal anemia and MCA-PSV should be followed serially instead. Intravenous immune globulin (IVIG) and plasmapheresis have also been used in some cases with a history of previous early mid-trimester loss due to RBC alloimmunization or markedly elevated titers, with a reported reduction in perinatal mortality and delay of the first IUT by 1.5 weeks. In contrast, one small randomized controlled trial found no additional benefit of IVIG when combined with IUT, compared with IUT alone, in cases of severe RhD alloimmunization.

IUT approaches and procedure-related (PR) risks

An intravascular approach, via the UV at the placental cord insertion (PCI), the intrahepatic vein (IHV) or a free loop of cord, has largely replaced intraperitoneal transfusion (IPT), first described in 1963. IPT may still have a role in very early pregnancy, as higher fetal loss rates are associated with intravascular transfusion at GA < 22 weeks. Rarely, an intracardiac approach may be used. In anatomically normal fetuses, the PR loss rate with IUT is approximately 1% ; this rate may vary, however, with GA, indication and operator experience. In the presence of structural abnormalities or hydrops, loss rates are reportedly 7% and 25%, respectively. PR risks include bleeding from the needle puncture site and fetal heart-rate decelerations, which are usually self-limiting and have been reported in up to 20–30% and 5–10% of procedures, respectively. In one series evaluating outcomes with IUT, performed mostly using a PCI approach, 3.1% of procedures had complications, including preterm prelabor rupture of membranes, infection, emergency Cesarean section, and IUFD or NND, with an overall loss rate of 1.6% per procedure. Preterm birth < 37 weeks was found to occur in 3.5% of cases and only in patients requiring multiple (more than three) IUTs. Fetal bradycardia and abandoned procedures were more common when a free loop of cord was targeted compared with IHV or PCI approaches.

Although IHV and PCI approaches are preferred over a free loop of cord, superiority of either IHV or PCI has not been demonstrated consistently. Ultimately, the choice depends on operator preference and experience. Advantages of the IHV approach include avoidance of arterial puncture and secondary vasospasm and cord tamponade, less FMH and success rates in the region of 90%. Furthermore, if intraperitoneal bleeding occurs, it is usually self-limiting and functions as an IPT. We perform > 70% of IUTs via the IHV and find this route particularly useful in multiple pregnancies or at advanced gestational ages when the placenta is posterior.

Fetal paralytic agents

Fetal paralytic agents, such as rocuronium, atracurium and vecuronium, are particularly useful if a prolonged or difficult procedure is anticipated. Paralysis may reduce the risk of cord complications, such as arterial spasm, hematoma or excessive bleeding, all of which can result from needle dislodgement with fetal movement.

Volume of transfusion

The volume of transfused blood depends on the estimated fetal weight, donor and fetal pretransfusion and target Hb/Hct, presence of hydrops and fetoplacental blood volume. Some authors caution against transfusing, during a single IUT, volumes > 20 mL/kg, corresponding to approximately 20% of the fetoplacental blood volume, as this may be associated with increased fetal mortality, related to circulatory overload. In our experience, the following formulae provide fairly reliable estimates of the volume of blood needed for IUT:

- intravascular transfusion (IVT) = (target Hb – fetal Hb) × fetoplacental blood volume / (donor Hb – target Hb);
- intraperitoneal transfusion (IPT) = (GA in weeks – 20) × 10 mL.

To avoid excessive transfusion and polycythemia, approximately two-thirds of the calculated volume should be transfused, followed by FBS to determine the final volume needed for IUT. Our target Hb level is 17 g/L, in non-hydropic fetuses.

Fetal anemia and hydrops fetalis: special considerations for IUT

Several studies have demonstrated worse outcomes following IUT in hydropic compared with non-hydropic fetuses, possibly due to their reduced cardiac reserve and increased susceptibility to volume overload. In a review of 80 fetuses that were hydropic secondary to RBC alloimmunization, which underwent IUT, the survival rate overall was 78% (98% in mild and 55% in severe hydrops). Reversal of hydrops occurred in 65% of cases overall, and only 40% of persistently hydropic fetuses survived. In practice, we do not raise the Hb/Hct more than four-fold in severely anemic, hydropic fetuses during a single IUT, as this has been found to be a predictor of fetal loss. Instead, we will perform a second procedure within 1–2 days if necessary to reach the target Hb/Hct.

Management after first IUT

There are no clear guidelines regarding fetal monitoring following IUT; however, weekly assessment of fetal wellbeing and MCA-PSV Doppler is reasonable.
Serial IUTs
Timing of subsequent IUTs is debatable, particularly since the use of MCA-PSV to predict fetal anemia becomes less reliable after several IUTs, with false-positive rates of 14%, 37% and 90% for the detection of 95% of severely anemic fetuses following the first, second and third IUT, respectively. As the rise in MCA-PSV in anemic fetuses likely reflects a hyperdynamic circulation due to decreased blood viscosity, the reduced accuracy of MCA-PSV following IUT may be related to altered properties of fetal blood, when admixed with adult blood cells, which have a lower viscosity. Furthermore, due to the replacement of fetal RBCs with adult RBCs following IUT, the concentration of fetal Hb, which has a higher affinity for oxygen, is reduced, thus lowering the total arterial oxygen concentration in the fetal circulation. Some authors have reported higher MCA-PSV thresholds for the diagnosis of severe anemia following IUT, speculating that this may be explained by a compensatory rise in cerebral blood flow, related to lower total oxygen carrying capacity and oxygen tissue delivery of transfused blood and the lower viscosity of adult RBCs. However, established cut-offs for diagnosis of fetal anemia following serial IUTs have not yet been defined. Alternatively, the timing of subsequent IUTs may be based on the anticipated decline in fetal Hb, 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 IUT intervals, respectively; or a decline of 1%/day in fetal Hct. Others have suggested transfusing empirically at 10 days, 2 weeks and 3 weeks, for second, third and subsequent IUTs, respectively.

Special considerations for management of TAPS
The ideal treatment of TAPS is laser ablation of the placental vascular anastomoses. However, if this is not possible, another option is to transfuse the anemic donor twin. This can result in worsening polycythemia for the recipient, especially with serial transfusions; this can be counteracted by hemodilution using partial exchange transfusions.

Timing of delivery
The therapeutic goal in managing RBC-alloimmunized pregnancies should be to enable delivery, close to term, of a healthy neonate who requires neither exchange transfusion nor prolonged phototherapy. In stable pregnancies that have undergone three or more IUTs, a final IUT at 34–35 weeks, with delivery 3–4 weeks later, is reasonable, unless other indications for delivery arise prior to this.

Short-term outcome following IUT
Neonatal survival overall, in the era of IUT, is 84%; 70% in hydropic and 94% in non-hydropic fetuses. The main short-term neonatal complications are related to hyperbilirubinemia requiring phototherapy or exchange transfusion, as well as thrombocytopenia, anemia and cholestasis. In the LOTUS (LONG-Term follow-up after intra-Uterine transfusionS) study, which evaluated short- and long-term neurodevelopmental outcome after IUT for alloimmunization, 17.5% of infants were delivered <35 weeks, with most delivering between 32 and 35 weeks. Severe neonatal morbidity included: respiratory distress syndrome (2.4%), necrotizing enterocolitis (1.0%), sepsis (5.8%), perinatal asphyxia (3.8%) and severe cerebral injury (1.7%). When outcome of neonates delivered ≥36 weeks was compared between those treated with and without IUT, phototherapy was required for shorter periods in those who had been transfused in utero; however, the exchange transfusion rate was similar in both groups and was required in nearly 70% of cases. Late or ‘hyporegenerative’ anemia presenting up to 3 months after birth has been described in association with HDFN, with nearly 30% of these infants requiring a RBC ‘top-up’ transfusion. Reticulocyte count at birth is inversely related to the number of top-up transfusions required, suggesting that suppression of erythropoiesis is the primary underlying mechanism.

Long-term outcome following IUT
Nearly 25% of alloimmunized mothers form additional antibodies following IUT, despite utilization of Rh- and Kell-matched blood products.

Neurodevelopmental outcome following IUT was normal in 95% of children assessed at a median age of 8.2 years in the LOTUS study. Cerebral palsy, severe developmental delay and bilateral deafness were detected in 2%, 3% and 1% of children, respectively. Factors independently associated with neurodevelopmental impairment included severe hydrops, number of IUTs and severe neonatal morbidity.

Outcome in hydropic alloimmunized fetuses following IUT is variable. In the LOTUS study, severe fetal hydrops was present in nearly 30% of children with, vs 6% of children without, neurodevelopmental impairment. When Harper et al. evaluated long-term neurodevelopmental outcome in 18 hydropic fetuses, they found that death or major morbidity occurred in 22%. Of 16 hydropic survivors, 13 were normal neurodevelopmentally at a median age of 10 years, and those with sequelae had other contributing factors, particularly prematurity. Long-term outcome in hydropic fetuses secondary to PB19 infection is less favorable, with a survival rate of 67–84%, suggesting that the virus may induce neural toxicity directly. Nagel et al. evaluated 24 fetuses that were hydropic due to PB19 and which underwent IUT; of 16 survivors, one third demonstrated delayed psychomotor development. In another series, evaluating 44 hydropic fetuses followed for a median of 5 years, survival was 73% and severe neurodevelopmental impairment was noted in three children.
RBC alloimmunization is the most common cause of fetal anemia, followed by PB19 infection and, more rarely, hemoglobinopathies, FMH, fetal and placental tumors and complications of monochorionic placentation. The non-invasive prediction of fetal anemia by Doppler evaluation of MCA-PSV measurements with a maternal–fetal medicine specialist with expertise in FBS and IUT is indicated when MCA-PSV measurements are ≥ 1.5 MoM. Baseline maternal investigations should include blood group and screen, testing for infectious serologies and FMH, and detailed placental and fetal ultrasound. If fetal blood is sampled, it should be tested for blood group and screen, Hb/Hct, platelet and reticulocyte count, hemolysis and viral infections. Rare causes may be evaluated in conjunction with hematology and genetics. FBS and IUTs can be performed by an intravascular, intraperitoneal or intracardiac approach. The intravascular approach is most common, preferably via the PCI or IVH, rather than a free loop of cord, in order to minimize the risk of fetal complications. Since the introduction of FBS and IUT, fetal survival has been reported at 85–90%3,88 and is approaching 97% for RBC alloimmunization in experienced centers103, with excellent long-term neurodevelopmental outcome even in the context of severe fetal hemolytic disease4.

REFERENCES


