Fetal anaemia

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Abstract

Fetal anaemia is a relatively rare occurrence, but it carries a risk of significant fetal morbidity and mortality. The most common causes of fetal anaemia are haemolytic disease of fetus and newborn and parvovirus B19 infection. The only diagnostic test for fetal anaemia is fetal blood sampling, but this is an invasive test with associated risk of miscarriage, preterm membrane rupture or intrauterine fetal death. Therefore it is only performed if there is a strong suspicion of fetal anamia based on the patient's history and ultrasound findings of raised peak systolic velocity in middle cerebral artery and/or fetal hydrops. The treatment for fetal anaemia is symptomatic rather than curative in most of the cases. In severely anaemic fetuses intrauterine blood transfusion is undertaken which corrects the anaemia but does not deal with the underlying cause. The aim of this intervention is to reach the gestation when the delivery is safer.

Keywords Antibodies; fetal anaemia; fetomaternal haemorrhage; haemolytic disease of fetus and newborn; hydrops; intrauterine transfusion; parvovirus B19

Introduction

Fetal anaemia is a relatively rare occurrence, but it carries a risk of significant fetal morbidity and mortality. Broadly speaking, fetal anaemia is caused by one, or a combination, of the following problems: a failure of red cell production, accelerated red cell destruction and/or loss of red blood cells (bleeding). The most common causes of fetal anaemia are maternal alloimmunisation and Parvovirus B19 infection. However, there are many other less common causes as summarised in Box 1.

Causes of fetal anaemia

Haemolytic disease of the fetus and newborn

Haemolytic disease of the fetus and newborn (HDFN) or red cell alloimmunisation is the most common cause of fetal anaemia. It is caused by transplacental transfer of maternal alloantibodies directed against incompatible fetal red blood cell (RBC) surface antigens inherited from the father. The antibodies bind to the surface antigens of the fetal erythrocytes and mark them for destruction in the fetal spleen. Anaemia develops if the fetal erythropoiesis cannot compensate for the loss of red blood cells.

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Causes of fetal anaemia

Accelerated red blood cell breakdown (haemolysis)
Haemolytic disease of fetus and newborn (HDFN)*
Red cell membrane defects and enzyme disorders
Haemoglobinopathies (thalassaemia)

Reduced red blood cell production (haematopoesis)
Fetal infection (parvovirus B19, CMV toxoplasmosis, syphilis)
Fetal bone marrow disorders (e.g. Fanconi anaemia, Diamond—Blackfan anaemia, congenital leukaemia)
Rare metabolic disorders (e.g. lysosomal storage diseases)
Kell alloimmunisation*

Red blood cell loss (haemorrhage)
Fetomaternal haemorrhage
Twin anaemia-polycythaemia sequence (TAPS)
Co-twin death in monochorionic twin pregnancies
Fetal and placental tumours (e.g. sacrococcygeal teratoma, placental chorioangioma)
Vasa previa

* Kell alloimunisation causes fetal anaemia by dual action — haemolysis and reduced haematopoiesis (see text for more details).

Box 1

HDFN can range from mild anaemia to fetal hydrops antenatally and from hyperbilirubinemia to kernicterus in the newborn.

There are over 300 RBC surface antigens identified and divided into groups (e.g. Rhesus, Kell, Duffy, Kidd, MNS). In cases of maternal alloimmunisation to these antigens most of the antibodies will not cause significant HDFN. There are over 45 antigens in the Rhesus group alone and most commonly implicated in HDFN are D, C, c, E and e.

The incidence of RhD alloimmunisation has reduced dramatically since the introduction of anti-D prophylaxis. The anti-D immunoglobulin is given after any potential sensitising event during pregnancy (e.g. antepartum haemorrhage, invasive procedure, abdominal trauma, external cephalic version) and after pregnancy (e.g. delivery, miscarriage, ectopic pregnancy). It is also administered routinely in the third trimester as a single dose between 28 and 30 weeks or split in two doses at 28 and 34 weeks.

Kell is another important group of antigens as it is associated with severe, often early onset anaemia in the fetus and antibody titres do not correlate well with the severity of the disease. Unlike alloantibodies to other antigens, anti-K (Kell) antibodies contribute to the severity of fetal anaemia by suppressing fetal erythropoiesis at the level of erythroid progenitor cells in addition to causing haemolysis.

ABO incompatibility between the mother and the fetus is common but usually only causes mild to moderate HDFN.

HDFN is unlikely to manifest in the first pregnancy unless maternal sensitisation occurred before pregnancy (e.g. following antigen incompatible blood transfusion or an organ transplant) as the maternal antibodies that develop at the time of first contact with the antigen are of IgM type that cannot cross the placenta. IgG antibodies are capable of crossing the placenta but usually take longer time to develop.

If maternal antibodies are detected during pregnancy the first step is to determine paternal antigen status (if possible). If the father is negative for the implicated antigen, the fetus will not be affected. If the implicated antigen is detected in the father and he is homozygous, the fetus would have inherited the antigen and is under increased risk of developing anaemia. If the father is heterozygous, there is a 50% chance that the fetus did not inherit the antigen. In this case, as well as in cases where it is not possible to test the father, or paternity is uncertain, fetal antigen status can be predicted from maternal blood with cell-free fetal DNA (cffDNA) testing for D, c, C, e, E and Kell antigens and the recently reported accuracy is 100% for each (95% CI 99–100%).

In pregnancies at risk of HDFN, antibody levels will be monitored and referral made to fetal medicine unit if the levels are significantly raised. Table 1 lists the RBC antibodies which have been most commonly associated with HDFN, and the levels of these at which fetal ultrasound surveillance should be commenced. Anti-D and Anti-c antibodies are the only antibodies that can be quantified and reported in IU/ml. All other antibodies are assessed by titration and the concentration is expressed as the number of serial dilutions of maternal serum required until the binding reaction is lost. The greater the number of dilutions required, the higher the starting level of antibodies. Titres are expressed as 1 in 2 (2), 1 in 4 (4), 1 in 8 (8), 1 in 16 (16), 1 in 32 (32) etc.

Anti-D, Anti-c and Anti-K antibodies are most likely to cause severe fetal anaemia, and levels should be checked every 4 weeks until 28 weeks and fortnightly thereafter. Levels of the other antibodies listed, if detected at booking, need to be repeated at 28 weeks and referral for fetal surveillance is only necessary if the titre reaches 32 or more.

Antenatal monitoring and treatment of HDFN are discussed below. The neonatologists should be informed in advance of delivery of all babies being born to women with clinically significant red cell antibodies, regardless of the levels, as there is increased risk of neonatal jaundice even if significant anaemia did not develop antenatally.

Fetal infections

The second most common overall cause, and the most common infectious cause, of fetal anaemia is parvovirus B19 infection also known as fifth disease, erythema infectiosum, or ‘slapped cheek syndrome’. Outbreaks in school-aged children are common in late winter and spring months. It is a highly infectious disease caused by a single-stranded DNA virus that spreads by respiratory droplets and has an incubation period of 7–14 days. It is a self-limiting disease which presents with a flu-like symptoms and a characteristic erythematous facial rash in children. It is mostly asymptomatic in adults with arthropathy as most commonly reported symptom.

Once acquired, infection provides lifelong immunity for most people which is confirmed by the presence of the IgG antibodies to the Parvovirus B19 which are found in about half of pregnant women. In pregnant women infected with Parvovirus B19, the risk of vertical transmission is approximately 30%.

Parvovirus causes pancytopenia by destroying blood cell precursors in the bone marrow and arresting haematopoiesis. Fetal anaemia can be profound and lead to hydrops and intrauterine demise. In addition to this, the virus can cause fetal hepatitis and myocarditis that aggravates the cardiac failure. Parvovirus B19 is not known to cause congenital abnormalities. The infection is diagnosed by detecting positive IgM antibodies in the maternal blood.

The risk of fetal loss before 20 weeks has been reported as 11% and after 20 weeks it decreases to <1%. In cases of suspected fetal anaemia a single intrauterine transfusion can be enough to prevent the fetus from becoming very unwell whilst in milder cases of fetal infection management can be expectant. In both scenarios, a weekly follow-up should continue for at least 12 weeks after confirmed infection.

Even though fetal anaemia has been described in association with other fetal infections like cytomegalovirus, toxoplasmosis and syphilis, it is less common and less likely to require an intervention.

Red blood cell loss

Fetomaternal haemorrhage (FMH): if there is an interruption in the barrier between fetal and maternal circulation within the placental bed, fetal red blood cells can cross from the capillaries in the placental villi through the trophoblast layers into the intervillous space which belongs to the maternal circulation. Fetomaternal haemorrhage can be spontaneous or caused by trauma.

Most common red cell antibodies known to cause haemolytic disease of the fetus and newborn, and their lower threshold of significance

Antigen group	Antibodies	Threshold for surveillance	Risk of significant fetal anaemia
Rhesus	Anti-D	>4 IU/ml	High (severe HDFN)
	Anti-c	>7.5 IU/ml	High (severe HDFN)
	Anti-c + anti-E	c >7.5 IU/ml + E ≥1 in 32	High (severe HDFN)
	Anti-E, -e, -C, -Ce	≥1 in 32	Low, mainly in neonates
Kell	Anti-K	Any titre	High (severe HDFN)
Duffy	Anti-Fy^a, -Fy^b	≥1 in 32	Low, mainly in neonates
Kidd	Anti-Jk^a, -Jk^b	≥1 in 32	Low, mainly in neonates
MNS	Anti-M, -N, -S, -s, -U	≥1 in 32	Low, mainly in neonates
ABO	Anti-A, -B	—	Low

Table 1

The true incidence of FMH is unknown. In most pregnancies affected by spontaneous FMH fetal blood loss will be insignificant and unlikely to lead to fetal compromise.

The effects on the fetus will depend on the gestational age, blood loss volume and the rate of blood loss. Acute massive FMH is likely to present with immediate fetal circulatory collapse and intrauterine death or neonatal anaemia, hypovolemic shock, acidosis and neurological injury if the baby is born alive. In cases of chronic FMH of smaller volumes the development of fetal anaemia is gradual allowing more time for the compensatory mechanisms to kick in (increased fetal heart rate and cardiac output, haematopoiesis). Depending on the severity of chronic anaemia, fetal hydrops can develop and can lead to intrauterine demise if undetected and untreated.

Different authors have tried to define a cut-off for defining massive FMH by using thresholds of estimated volumes of fetal blood loss into the maternal circulation (ranging from 80 to 150 ml). As the total fetoplacental blood volume increases throughout the pregnancy the loss of the same volume of blood will not have the same effect in a term fetus compared to a second trimester fetus, for example. Therefore, these cut-offs are of no clinical value and the estimated blood loss volume should be compared to the calculated total fetoplacental blood volume and correlated with clinical findings.

Spontaneous FMH can be very difficult to diagnose antenatally and the first presentation is often reduction in fetal movements. This is a very subjective and non-specific sign and FMH can be easily missed if there are no other signs that would raise suspicion like history of abdominal trauma, sinusoidal CTG trace (see Figure 1) or incidental finding of ultrasound features of fetal anaemia.

The most common time for FMH is during birth, however if the bleed occurs after the cord has been clamped then there will be no consequence for the newborn.

Kleihauer–Betke test and flow cytometry are diagnostic and quantitative tests of FMH. Flow cytometry has greater accuracy but is more expensive and less widely available. Both tests can overestimate the size of the FMH if the mother has elevated levels of persistent HbF herself (which is particularly the case in the second trimester) or can underestimate FMH if ABO incompatibility or isoimmunisation against other red cell antigens means that fetal red blood cells are cleared more quickly from the maternal circulation.

If FMH is detected at preterm gestations where the risk of prematurity outweighs the risks of further FMH, it can be very difficult to monitor and manage these pregnancies due to the unpredictable nature of the condition.

Complications of monochorionic multiple pregnancies: monochorionic multiple pregnancies are associated with additional risks when compared to dichorionic gestations due to the vascular anastomoses within the placenta between the two (or rarely more) fetal circulations.

Twin to twin transfusion syndrome (TTTS) is caused by large unbalanced feto-fetal transfusion and manifests as hypovolemia in one twin (donor) and hypervolemia in the other (recipient), with no difference in haemoglobin values between them. However, isolated twin anaemia-polycythaemia sequence (TAPS) is a consequence of chronic low volume transfusion through small calibre (<1 mm) arterio-venous anastomoses causing anaemia in one fetus and polycythaemia in the other with no significant effect on their circulating blood volumes.

TAPS can develop spontaneously in up to 5% of monochorionic pregnancies but it is more common in pregnancies treated with fetoscopic laser ablation for TTTS. Post laser, it is caused by anastomoses that were not successfully coagulated (incidence reported to be as high as 16%).

The antenatal diagnosis of TAPS, according to a Delphi procedure expert consensus from 2020, relies on discordance of ≥1.0 MoM in peak systolic velocities in the middle cerebral artery (MCA-PSV) of each fetus or the combination of MCA-PSV ≥1.5 MoM in the anaemic twin and ≤0.8 MoM in the polycythaemic twin (see Figure 2).

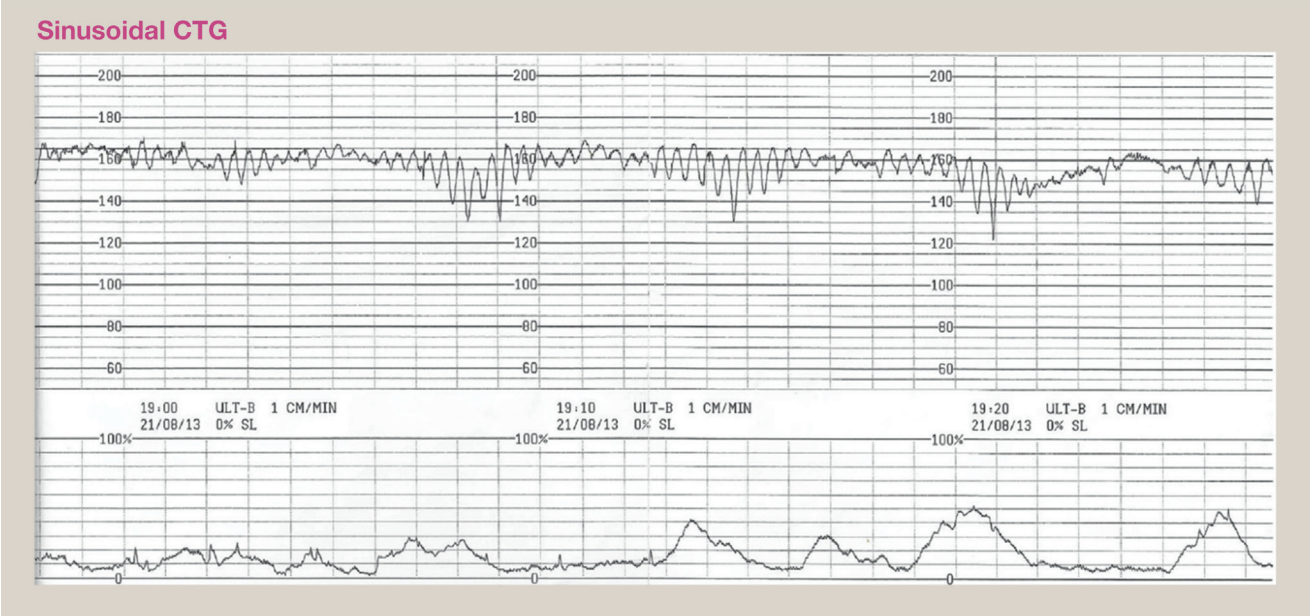

Figure 1

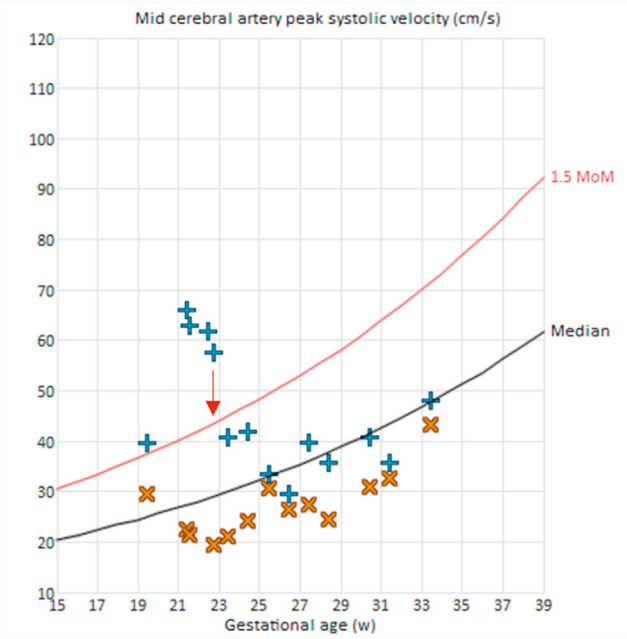

Figure 2 Middle cerebral artery peak systolic velocities in monochorionic twin pregnancy affected by TAPS plotted on a graph by Mari et al.: twin 1 (blue +) is anaemic and twin 2 (orange x) is polycythaemic. Red arrow represents the timing of the fetoscopic laser ablation to treat TAPS after which point there is normalisation of MCA-PSV of the anaemic twin.

There is no consensus on the best treatment for TAPS and the options include expectant management, delivery, fetoscopic laser ablation and intrauterine transfusion with or without partial exchange transfusion. The choice of treatment will depend on the gestation, severity of the anaemia and the experience of the fetal therapy centre. No option is without associated risks and further research is needed to recommend one option over another.

In cases of single twin demise in monochorionic twin pregnancies there is an acute transfusion from the high-pressure circulation of the surviving twin into the low-pressure circulation of the demised twin which can lead to co-twin death or neurological sequelae in survivors due to hypotension, hypovolaemia, ischaemia, and anaemia.

Vasa previa: vasa previa is defined as a fetal blood vessel running through the membranes in close proximity to the internal os of the cervix. The reported prevalence is 1 in 1200–5000 pregnancies. It is more commonly found in multiple gestations and in pregnancies with velamentous cord insertion and/or succenturiate placental lobes. The fetal blood loss from a ruptured vasa previa is acute and rapid with a high mortality rate, particularly if it happens outside of hospital setting.

As there is no universal screening for vasa previa, it often goes undetected prenatally and presents with painless bleeding associated with sudden fetal heart rate abnormalities following a spontaneous or artificial rupture of membranes, leading to urgent delivery via caesarean section if the fetus is still alive at the time of the presentation. For this reason, if detected antenatally, planned caesarean section at 34–36 weeks is recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 27b.

Fetal and placental tumours: although rare, sacrococcygeal teratoma is the most common fetal tumour and can be a cause of fetal anaemia as a result of haemorrhage and/or sequestration of erythrocytes within the tumour, particularly if it is large in size. Similarly, fetal anaemia can develop in pregnancies with large placental chorioangiomas.

In more recent years, there are reports of fetal interventions available in highly specialised fetal medicine centres (e.g. ultrasound guided laser coagulation of feeder blood vessels, radiofrequency ablation, open fetal surgery) that can be offered in severe cases with high risk of fetal demise without intervention. However, the current evidence is limited, and the outcomes vary.

Other causes of fetal anaemia

Haemoglobinopathies, bone marrow disorders, erythrocyte enzyme disorders and membrane defects can all cause fetal anaemia. The haemoglobinopathies are disorders of haemoglobin production. Alpha thalassemia is associated with most significant antenatal morbidity and mortality. Normal individuals have four working copies of the α-globin gene (αα/αα). Alpha thalassemia has four different types depending on how many of α-globin genes are missing and the most severe form with all four genes missing is called alpha thalassemia major or haemoglobin Bart (Hb Bart) syndrome in which no functional α-globin chains are produced. Due to abnormal haemoglobin molecule formation the fetus becomes hypoxic, develops cardiac failure and hydrops, and will inevitably die without intervention. Antenatal intervention by serial intrauterine transfusions remains ethically challenging as survivors require lifelong blood transfusions, or bone marrow transplant at a very early stage of life. Major growth deficiencies, complications from iron overload and neurodevelopmental delay are common.

Inherited red cell membrane disorders (e.g. hereditary spherocytosis, hereditary elliptocytosis) lead to rapid haemolysis due to abnormally shaped and more fragile erythrocytes. Red cell enzyme disorders, such as pyruvate kinase deficiency and G6PD deficiency, have also been implicated in rare cases of haemolytic fetal anaemia.

Fetal bone marrow disorders like Fanconi anaemia and Diamond-Blackfan anaemia are extremely rare but may cause fetal anaemia, neutropenia and thrombocytopaenia. They usually have other associated congenital abnormalities and implications. In rare cases of Trisomy 21 the fetus will develop anaemia and hydrops secondary to a transient myeloproliferative disorder.

Diagnosis of fetal anaemia

A patient could present with risk factors for fetal anaemia, such as being positive for red blood cell antibodies or declaring exposure to Parvovirus B19 infection, in which case they should be referred to a fetal medicine specialist for ultrasound screening for fetal anaemia. In other cases, suspicion of fetal anaemia can be raised from incidental scan findings (see below) and further investigations directed by the specific clinical presentation.

A detailed history and a thorough ultrasound assessment of the fetus are crucial steps in the diagnosis of fetal anaemia. However, it is important to note that the only truly diagnostic test is fetal blood sampling (FBS) if the level of suspicion is high.

Fetal anaemia could also present in a more dramatic fashion with fetal heart rate abnormalities on the CTG trace in a patient attending with reduced fetal movements. A sinusoidal CTG pattern is a rare finding associated with severe fetal anaemia that often requires urgent delivery (see Figure 1). This pattern can be difficult to distinguish from a benign pseudo-sinusoidal pattern usually associated with fetal sucking that rarely exceeds a duration of 30 minutes and is preceded and followed by a normal trace. Consequently, the CTG is not suitable as a tool for surveillance or diagnosis of fetal anaemia.

In the early stages of fetal anaemia, the only ultrasound marker can be increased peak systolic velocities in the middle cerebral artery (MCA-PSV). As the blood becomes less viscous and the oxygen supply to the organs decreases, cardiac stroke volume increases and the vasodilation occurs in the brain to prevent hypoxic injury, resulting in increased blood flow in the cerebral arteries.

This non-invasive method was introduced into practice following a publication by Mari et al. in 2000 and has been the gold standard in the screening of fetal anaemia ever since. The sensitivity of MCA-PSV in the prediction of moderate or severe anaemia in the publication is reported as 100% with a false positive rate of 12%.

Prior to this, serial amniocentesis was performed to screen for fetal anaemia by quantifying bilirubin levels in the amniotic fluid with spectrophotometry (expressed as the change in optical density at a wavelength of 450 nm (ΔOD_{450}) and plotted on Liley's chart). Oepkes et al. compared MCA-PSV detection of fetal anaemia to this method and found a sensitivity of 88%, specificity of 82% and an accuracy of 85% compared to sensitivity of 76%, specificity of 77% and an accuracy of 76% of the ΔOD_{450}. The other limitations of this test were risks associated with repeated invasive procedures and inability to detect anaemia from non-haemolytic causes.

The MCA-PSV measurement should be obtained in the absence of fetal movements as it can be falsely elevated otherwise. The axial section of the fetal brain is obtained at the level of the wings of the sphenoid bone and the MCA is identified with colour Doppler. The pulsed-wave Doppler gate is then placed at the medial third of the MCA, just as it emerges from the Circle of Willis and insonation angle should be as close to 0° as possible (see Figure 3a). The highest value is plotted on the chart and the anaemia is suspected if the PSV is above the threshold of 1.5 multiples of median (MoM) (see Figure 3b).

The indirect ultrasound signs of severe fetal anaemia are mostly features of heart failure (cardiomegaly, abnormal myocardial contractility, tricuspid regurgitation, reversed 'a wave' in ductus venosus and hepatosplenomegaly due to congestion) and/or fetal hydrops (abnormal accumulation of fluid in two or more fetal compartments) that include ascites, skin oedema, pleural and pericardial effusion, and only occur with very severe chronic fetal anaemia (see Figure 4). Placentomegaly and polyhydramnios can also be present.

These signs are non-specific as heart failure and fetal hydrops can be caused by a multitude of other maternal and fetal disorders that don't present with fetal anaemia (e.g. chromosomal/genetic abnormalities, cardiac defects, masses causing mediastinal compression). Fetuses with chronic mild to moderate anaemia can present with fetal growth restriction without the signs of hydrops.

Fetal blood sampling (FBS) is an invasive and highly specialised procedure that carries a risk of miscarriage, preterm membrane rupture or intrauterine fetal death. It should only be undertaken if there is a strong suspicion that the fetus is significantly anaemic.

Other specific investigations are guided by the patient's history and clinical findings and can include parental red blood cell antigen/antibody tests, infection screening, genetic testing, Kleihauer–Betke test and so forth.

Treatment of fetal anaemia

In the majority of cases of fetal anaemia, the treatment will be symptomatic rather than curative. The treatment will depend on gestational age and underlying cause (if known).

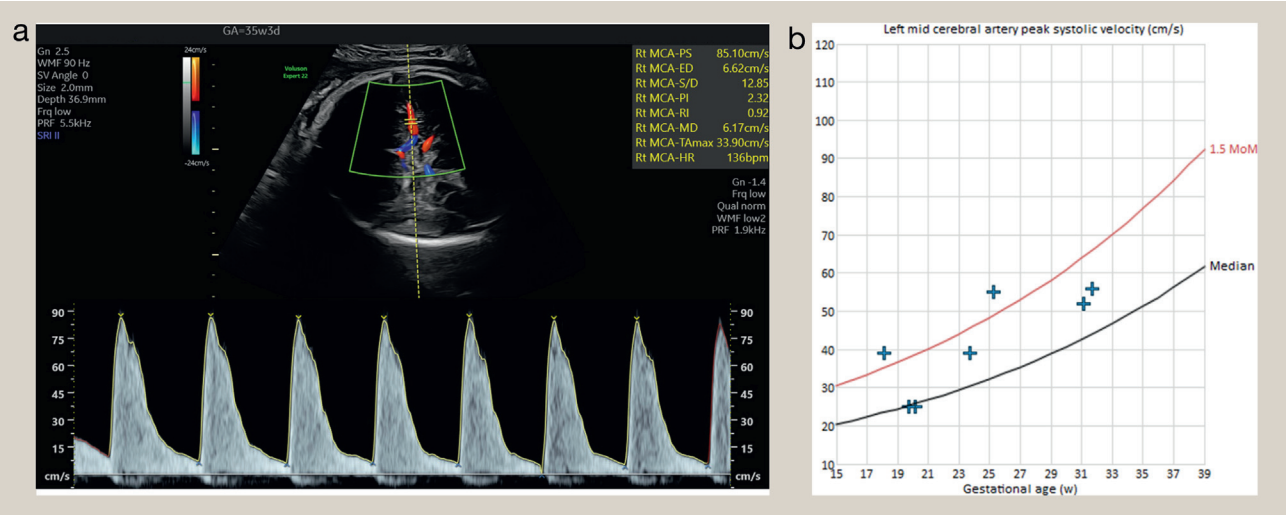

Figure 3 (**a**) Measurement of the middle cerebral artery Doppler peak systolic velocity (MCA-PSV). (**b**) MCA-PSV measurements taken from a pregnancy affected by HDFN and plotted on a graph by Mari et al. The elevated MCA-PSV levels are followed by intrauterine transfusions which then bring down the peak systolic velocities into the normal range.

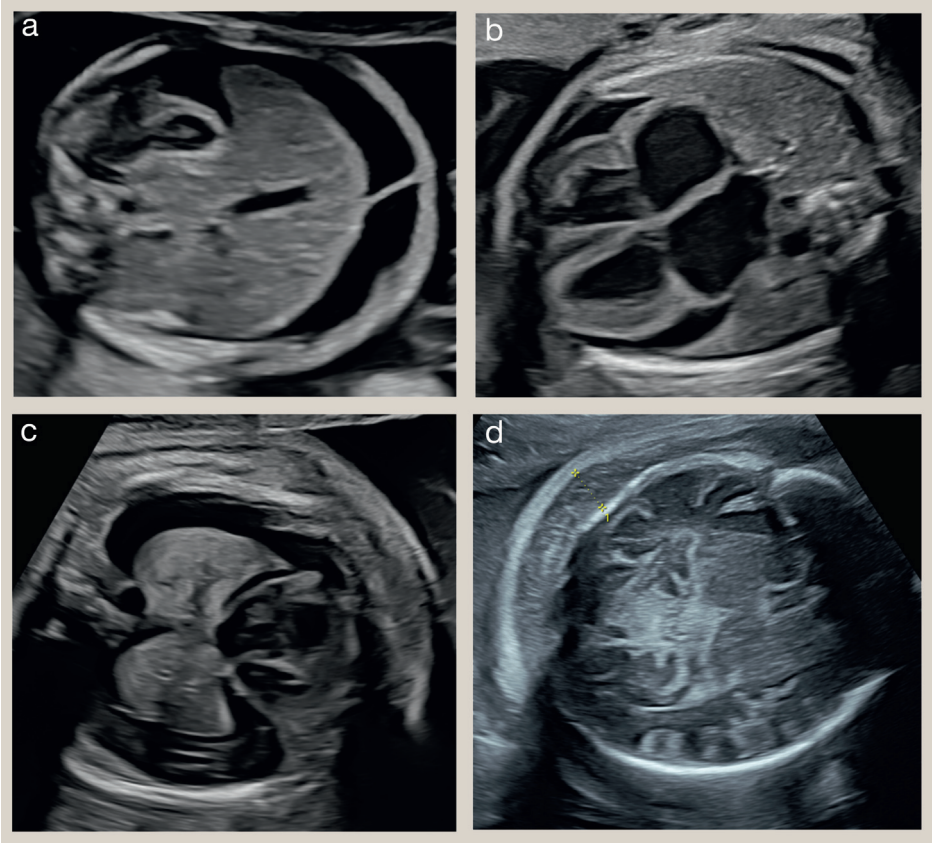

Figure 4 Ultrasound features of severe anaemia (signs of hydrops): (**a**) fetal ascites, (**b**) cardiomegaly and pericardial effusion, (**c**) bilateral pleural effusion and thoracic wall skin oedema, (**d**) scalp oedema.

Conservative management

In mild cases of fetal anaemia a conservative approach of monitoring fetal anaemia by serial ultrasound scans can be considered if the risks of intervention surpass the risks of significant fetal compromise without intervention.

Delivery

If fetal anaemia is detected at an advanced gestational age (≥34 + 0 weeks of gestation) and there are no signs of hydrops delivery should be considered. As mentioned above, in cases where fetal anaemia is suspected from an abnormal (sinusoidal) CTG trace an urgent delivery via caesarean section might be indicated.

The prognosis is poor in fetuses with fetal hydrops and intrauterine treatment might be a better option if it helps resolve the hydrops and improve the condition of the neonate at the time of birth.

Intrauterine transfusion

Following initial attempts of intrauterine transfusion (IUT) by performing open hysterotomy to gain access Liley described the first successful intraperitoneal fetal blood transfusion via a catheter inserted into the fetal abdomen guided by fluoroscopy in 1963. IUT has evolved greatly since then and has become a much safer and less invasive procedure, but still not without risks (see Box 2) and requiring a high level of skill.

Ultrasound-guided intrauterine fetal blood transfusion is now a first line symptomatic treatment for significant fetal anaemia, regardless of the underlying cause. The IUT is usually performed as an outpatient procedure under local anaesthesia in aseptic conditions. Sedation can be offered to the mother beforehand.

If the fetus is viable, it is good practice to liaise with delivery suite team prior to commencing the transfusion in case of complications requiring emergency caesarean section.

To reduce the risk of needle dislodgement (particularly for intrafetal access) the fetus can be temporarily paralysed with short-acting agents like vecuronium in a dose of 0.1 mg per kg of estimated fetal weight, given to the fetus intramuscularly or intravenously.

Short- and long-term complications of intrauterine transfusion (IUT)

Fetal loss in non-hydropic cases (1%)
Fetal loss in hydropic cases (up to 25%)
Preterm membrane rupture (0–1.3%)
Chorioamnionitis (0–1.0%)
Fetal heart rate abnormalities (mostly self-limiting) (5–10%)
Emergency caesarean section (secondary to persistent FHR abnormalities)
Perinatal asphyxia
Neonatal death
Formation of new red cell antibodies
Further stimulation of alloimmune antibody response

Box 2

The donor blood for fetal blood transfusion is specially prepared (warmed, irradiated, CMV/HIV negative), usually 0 Rh D negative unless fetal blood group is known, and crossmatched to maternal antibodies. Red blood cells are packed to a haematocrit of 70–80% to reduce the volume of the transfused blood and the risk of volume overload.

Fetal blood sampling is performed prior to blood transfusion to obtain the starting fetal haemoglobin/haematocrit value needed for the calculation of the required transfusion volume. This cannot be done in early gestations which instead must rely on intraperitoneal transfusion. The calculation is made using estimated fetoplacental volume (dependant on gestation and/or estimated fetal weight), starting haematocrit (estimated or measured), goal haematocrit and the donor haematocrit.

The preferred access to the fetal circulation for the IUT is into the umbilical vein at the placental cord insertion site if feasible. However, if the placental cord insertion is not accessible (e.g. posterior placenta) blood can be transfused intravascularly into the intrahepatic portion of the umbilical vein or given extravascularly into the fetal peritoneal cavity where it gets absorbed through the lymphatic system into the fetal circulation. The latter will take longer to improve the fetal haemoglobin levels and can be impeded by the presence of ascites/hydrops. Access to the umbilical vein in a free loop of cord is rarely used due to a higher chance of needle dislodgement, increased risk of fetal heart rate abnormalities and bleeding from the puncture site. An intracardiac approach is reserved for extreme circumstances where all the other options have been excluded (e.g. severe fetal hydrops at an early gestation).

The blood is given slowly whilst monitoring the flow, signs of extravasation and fetal heartbeat by the ultrasound. The potential complications of IUT are listed in Box 2. Higher fetal loss, complication and failure rates are associated with fetal hydrops, early gestational age, failure to use fetal paralytic agents, transfusion into a free loop of cord, operator inexperience and severity of fetal anaemia.

Depending on the cause of anaemia, one transfusion may suffice (usually the case with Parvovirus infections), or serial IUTs may be required, particularly in cases of HDFN. Post-transfusion decline in haematocrit is reported to be 1–2% per day. Timing of subsequent transfusions is individualised to each patient and can be empirical (usually planned for every 2–3 weeks) or based on MCA PSV measurements. However, there is suggestion that MCA-PSV becomes less reliable with increasing numbers of IUTs performed, perhaps due to the different properties of the transfused adult red blood cells.

Other treatments

Use of intravenous immunoglobulins (IVIg) and plasmapheresis have been frequently documented as adjunctive therapies for severe fetal haemolytic disease caused by red cell antibodies but there is not enough evidence to support routine use of either of these treatments.

Outcomes

The outcome of fetal anaemia and treatment with IUT is very much determined by the underlying cause. Good quality data are only available in HDFN. The LOTUS study published the outcomes of over 1200 IUTs performed in 4451 fetuses over a 20-year period. More than 95% of children had normal neurodevelopmental outcomes, with hydrops being the key risk factor for poorer long-term outcomes, emphasising the need for early detection and treatment of fetal anaemia. Severe developmental delay, cerebral palsy and bilateral deafness were found in 3%, 2% and 1% of children respectively. These outcomes may be secondary to prematurity, perinatal asphyxia or kernicterus. 26% of the fetuses in this study were hydropic at the time of their first transfusion, also illustrating that despite very low fetal haemoglobin levels a normal outcome is more likely. The long-term outcome of hydropic fetuses with parvovirus infections would seem to be less good, with normality predicted for two thirds. It is possible that the virus has a directly neurotoxic effect.

Case studies

Case 1

A 28-year-old lady was referred to a tertiary fetal medicine unit at 25 weeks for suspicion of significant fetal anaemia. She was known to have anti-D antibodies and the levels were rising. The father of the child was homozygous for D antigen, therefore the fetus was predicted to be RhD positive. On assessment, there were signs of hydrops (ascites, scalp oedema), cardiomegaly and the MCA-PSV was 1.69 MoM for the gestation. The patient had an urgent IUT on the same day and the starting haemoglobin (Hb) was 31 g/L. 90 ml of donor blood was transfused and the Hb was 97 g/L at the end of the procedure. She was seen a week later and a severe bilateral ventriculomegaly was noted. MCA-PSV was still >1.5 MoM with signs of hydrops. Another IUT was performed on the day and Hb was 69 g/L at the start and 142 g/L at the end after this second transfusion of 80 ml of blood. Another scan was performed four days later and the signs of hydrops were resolving, but the ventriculomegaly was progressing (see Figure 5a). Urgent MRI of the fetal brain was arranged and it showed significant brain abnormalities associated with hypoxic damage due to severe anaemia (severe bilateral ventriculomegaly, cortical thinning and gross global multicystic encephalomalacia – see Figure 5b). Due to the high risk of neurodisability the parents decided not to continue with the pregnancy and had termination of pregnancy at 29 weeks gestation.

Case 2

A 36-year-old lady was referred to fetal medicine unit at 22 weeks for suspected fetal anaemia and history of maternal viral symptoms following slapped cheek disease in her child 12 weeks ago. The scan showed mild ascites, pericardial effusion and skin oedema. There was cardiomegaly with biventricular hypertrophy, tricuspid regurgitation and pulmonary artery stenosis. MCA-PSV was 2.85 MoM. An urgent IUT was performed. Pre-transfusion Hb was 12 g/L and it increased to 123 g/L after transfusion of 35 ml of blood. Parvovirus B19 infection was confirmed by PCR in the fetal blood sample. The patient was seen a week later and MCA-PSV was within normal range with resolving signs of hydrops. Fetal brain MRI was done at 29 weeks to exclude hypoxic damage and the intracranial anatomy was

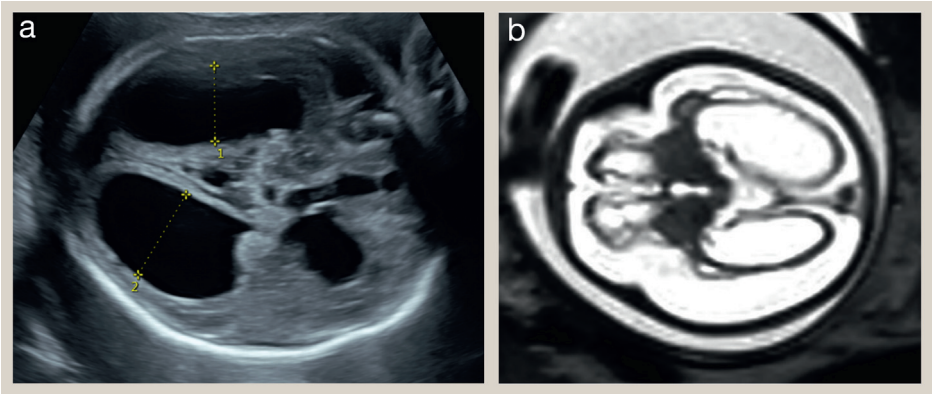

Figure 5 (**a**) Ultrasound image of bilateral ventriculomegaly caused by hypoxic brain injury, (**b**) MRI image of the fetal brain in the same patient.

normal. Ultrasound surveillance continued until 36 weeks. There was reversal in cardiac changes secondary to prolonged fetal anaemia and no further intervention was required. A healthy girl was born at 38 weeks. ◆

FURTHER READING

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Practice points

- The consequences of fetal anaemia for the fetus will depend on the underlying cause, gestational age at the time of onset, severity, and fetal adaptive mechanisms
- Most common causes of fetal anaemia are haemolytic disease of fetus and newborn and Parvo B19 infection
- If there are risk factors or suspicion of fetal anaemia from the ultrasound findings the patient should be referred to a fetal medicine unit able to perform intrauterine transfusion
- Ultrasound measurement of middle artery peak systolic velocity is the gold standard for screening and monitoring fetal anaemia
- The only diagnostic test for fetal anaemia is fetal blood sampling
- Intrauterine transfusion is a highly effective symptomatic treatment for fetal anaemia but it requires subspecialist skills and is not always appropriate, depending on the cause. Some cases of fetal anaemia can be managed conservatively, or by earlier delivery