Fetal anaemia

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Abstract

Fetal anaemia is a relatively rare occurrence with varied aetiology. Although it may cause reduced fetal activity, or the development of hydrops, or be detected by chance on ultrasound scanning, it may also present with stillbirth or neonatal anaemia, with or without haemodynamic compromise. Broadly speaking, anaemia is caused by one, or a combination, of the following problems: (i) a failure of red cell production; (ii) accelerated red cell destruction; (iii) loss of red blood cells (bleeding). This is also the case for the fetus. Anaemia caused by an acute loss of blood will be accompanied by hypotension and shock, and a significant risk of sudden death, or critical neurological and visceral ischaemia. Conversely, the chronic development of anaemia in the fetus carries no risk of haemodynamic compromise, but will eventually lead to high output cardiac failure, hypoxia, metabolic acidosis and hydrops. The management of fetal anaemia will be determined by the underlying cause, the severity, and the gestation. A conservative 'wait and see' approach is suitable in select cases, whereas immediate delivery is mandated in others. Intrauterine transfusion is a highly successful treatment, but is not always considered appropriate, carries some degree of risk, and requires subspecialist skills.

Keywords fetal anaemia; fetomaternal haemorrhage; hydrops; intrauterine transfusion; kleihauer; parvovirus; peak systolic velocity; red cell alloimmunisation; TAPS

Causes of fetal anaemia

The causes of fetal anaemia are summarised in Table 1.

Fetomaternal haemorrhage (FMH)

FMH can be defined as the loss of fetal red blood cells across the trophoblast layer into the maternal circulation. Fetal placental vessels have a higher blood pressure than that of the intervillous space, and any breach in the villi will result in bleeding from fetus into its mother. Indeed, this is thought to occur in most pregnancies, although the volumes are usually clinically insignificant. In less than 1% of pregnancies is the volume 15 ml or more. Massive FMH has been defined as a loss of >80 ml or >150 ml, and this occurs in approximately 1 in 1000 and 1 in 5000 pregnancies respectively. However, these definitions are of little value because the impact on the fetus or newborn will depend on the gestation at which the FMH occurs, and the duration over which the blood is lost. The fetoplacental blood volume expands from approximately 30 ml at 20 weeks' gestation to 80–90 ml/kg at term. Larger bleeds will be tolerated less well at earlier gestations. Slow haemorrhage over a number of weeks will be tolerated better than the same total volume of blood loss occurring over a few minutes, which is likely to be associated with fetal hypotension, acute acidosis and ischaemia. It is not uncommon to see fetal haemoglobin levels of less than 50 g/L when fetal haemolytic disease or parvovirus infection are the cause. However, these babies usually do well in the long run, following intrauterine transfusion. They develop their anaemia gradually, and there is no haemodynamic compromise associated with it, as opposed to the hypotension occurring with a sudden and massive FMH.

FMH may result in reduced or absent fetal movements, a non-reassuring or sinusoidal CTG (see later), fetal growth restriction and/or hydrops, or stillbirth in the antenatal period, or neonatal anaemia, shock, acidosis and neurological injury after birth, depending on the scenario.

The exact pathophysiology of FMH is not well understood, although there are a number of situations which are recognised as risk factors (Table 2). 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 fetus or newborn. It is not known if breaches in the trophoblast layer can heal themselves, or what might make a small defect suddenly increase in size.

There are two well established methods of measuring the size of a fetomaternal bleed. The Kleihauer-Betke screen takes advantage of the fact that adult haemoglobin can be eluted from erythrocytes by acid, whereas fetal Hb is resistant to this. A maternal blood smear can be treated with acid and then stained with erythrosine B. Maternal erythrocytes appear as 'ghosts' on microscopy, whereas fetal red blood cells are stained cherry red. The fetal Hb containing cells can be counted manually, and a volume calculated using a simple formula. The test is labour intensive and rather imprecise, but nevertheless widely available. Flow cytometry is an alternative and more precise method. Fluorescently labelled monoclonal antibodies against HbF are mixed with the maternal blood sample and fluorescent cells (those containing HbF) are sorted and counted separately. The test is fast and more accurate, but not available universally, and often not out-of-hours. Both tests can overestimate the size of the FMH if the mother has elevated levels of persistent HbF herself, and can underestimate if ABO incompatibility or isoimmunisation against other red cell antigens means that fetal red blood cells are cleared more quickly from the circulation. Some fetal red blood cells may survive for a number of weeks in the maternal blood, so these tests do not allow estimates of the timing or duration of the FMH.

A sudden cessation or slowing of fetal movements is a relatively common warning sign of fetal anaemia, and performing a Kleihauer test, or an appropriate ultrasound scan (see later) when women present with concerns over fetal movements will occasionally diagnose the underlying cause as FMH. If a FMH is proven prior to delivery, the options are to observe, perform a cordocentesis/fetal blood transfusion, or deliver. Bleeds occurring at significantly preterm gestations will encourage fetal blood sampling and intrauterine transfusion, but even after the fetus is 'topped-up' with blood, there can be no assurance that another sudden, and possibly heavier, bleed will not occur. A number of small case series attest to the relative safety of transfusing the fetus in this situation, but there can be no guarantee that sudden intrauterine fetal death won't occur, and delivery at 34 weeks'

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Causes of fetal anaemia

Accelerated red cell breakdown
- Red cell alloimmunisation
- Red cell membrane defects and other congenital haemolytic anaemias
- Thalassaemia: alpha thalassaemia Major (B-thalassaemia)

Reduced red cell production
- Kell alloimmunisation
- Fetal infection: Parvovirus (CMV, syphilis, toxoplasmosis)
- Fetal bone marrow disorders: Fanconi anaemia, Diamond-Blackfan syndrome, congenital leukaemia/myeloproliferative disorders
- Rare metabolic genetic disorders eg lysosomal storage diseases, neonatal haemochromatosis

Red cell loss
- Fetomaternal haemorrhage
- TAPS
- Co-twin death
- Vasa praevia
- Fetal and placental tumours eg sacrococcygeal teratoma, placental chorangioma

Table 1

gestation is justified. Significant FMH after 34 weeks delivery may be optimally managed with steroids and elective preterm birth. Women who are RhD negative will of course need sufficient Anti-D prophylaxis to protect them against isoimmunisation, although this may be too late if the fetal bleeding has occurred over a number of days.

Managing subsequent pregnancies is no less daunting. Although the recurrence risk might be expected to be low, there are cases reported of subsequent pregnancies also being affected by FMH and requiring intrauterine transfusion. It is tempting to offer serial Kleihauer tests, MCA Dopplers and early delivery to women who have experienced significant antepartum unprovoked FMH in a previous pregnancy however there is no good evidence to support this, and Doppler scanning does carry a false positive risk. Despite this, most women will feel the need for some form of increased fetal surveillance.

Red cell alloimmunisation

Women who have been pregnant before, received a blood transfusion, or who have been the recipient of a transplanted organ, may have been exposed to red blood cell antigens not expressed by their own erythrocytes. If this is the case, they may have alloimmunised against these red cell antigens and generated antibodies against them which can subsequently reach the fetus by transportation across the placenta. If the fetal red cells expresses this red cell antigen then antibody binding will result in haemolysis. If fetal haematopoiesis fails to keep up with this red cell breakdown, fetal anaemia will occur. Red cell antibodies are routinely screened for and found in approximately 1% of pregnancies, although in less than half (0.4%) are they clinically significant, and in even fewer cases is the resulting haemolysis sufficient to result in significant fetal anaemia. Table 3 lists the red cell antibodies which have most commonly been associated with fetal anaemia, and the levels of these at which fetal ultrasound surveillance should be instituted for anaemia (see later).

Anti-D, Anti-c and Anti-K antibodies are the most likely to cause severe fetal anaemia, and levels should be checked every 4 weeks to 28 weeks' gestation and fortnightly thereafter. The fetus is only at risk of haemolytic anaemia if it actually expresses the red cell antigen recognised by the maternal antibody. Reliable non-invasive maternal blood tests are now available for all three red cell antigens, allowing fetal status to be determined securely in cases of uncertain paternity, inability to test paternal blood, or paternal heterozygosity for the antigen in question. Levels of the other antibodies listed, if detected at booking, need only be

Causes of fetomaternal haemorrhage

- Normal birth
- Manual removal of placenta
- Caesarean section
- Abruption
- Blunt trauma
- Pre-eclampsia
- ECV
- Invasive prenatal testing (CVS/amniocentesis)
- Placental tumours

Table 2

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

Antibodies causing haemolytic disease in the fetus and newborn	
Anti-D	>4iu/ml
Anti-c	>7.5 iu/ml
Anti-K (Kell)	Any titre
Anti-E,-C,-Ce, -Fy^a, -Jk^a	Titre greater than 32
Antibodies causing only newborn haemolytic disease	
Anti-e,	
Anti-Fy^b	
Anti-S, -s	
Anti-U	
Anti-M, −H, -G	

Table 3

repeated at 28 weeks and referral for fetal surveillance is only necessary if the titre reaches 32 or more. The paediatricians should be informed in advance of delivery of all babies being born to women with clinically significant red cell antibodies, whatever level has been reached. The baby may not develop in utero anaemia, but may nevertheless be at risk of neonatal jaundice following delivery. Anti-K (Kell) antibodies are worthy of particular mention. They do cause haemolysis of fetal red cells bearing the Kell antigen, but they also suppress haematopoiesis, thereby causing fetal anaemia by two mechanisms. No lower 'safe' titre is recognised, so if the father of the baby is Kell positive (usually heterozygous), or if his Kell status is unknown, or there is any doubt over paternity, maternal blood should be sent for non-invasive testing of the fetal Kell status to determine if it is at risk, or not.

Complications of monochorionic twinning

In the majority of monochorionic placentae vascular anastomoses within and on the surface of the placenta connect the circulations of the twins, allowing bidirectional blood flow. Depending on the number and proportion of arteriovenous, arterio-arterial and veno-venous anastomoses, flow across the equator of the placenta may be balanced, or there may be a net flow towards one twin (the recipient) and away from the other (the donor). This twin to twin transfusion causes growth discrepancy, the oligo/polyhydramnios sequence, activation of the fetal renin-angiotensin system, high output cardiac failure and cardiac dysfunction in the recipient, discordant haemoglobin values, renal impairment in the donor and ultimately hydrops and fetal death. This is known as Twin-to-Twin Transfusion Syndrome (TTTS). However, much smaller calibre (<1 mm) inter-twin anastomoses are responsible for a subtle chronic variant of this known as Twin Anaemia-Polycythaemia Syndrome (TAPS) which is not associated with discrepancies in amniotic fluid volumes between the twins. Although TAPS may complicate an otherwise normal MCDA twin pregnancy, it is most commonly seen following selective laser ablation of major A-V anastomoses for TTTS. These small vessels allow the slow leakage of blood from one twin into the other, potentially leading to very discordant haemoglobin values at birth (up to 80 g/L). It is diagnosed when one twin becomes polycythaemic (mean systolic velocity in the middle cerebral artery is <1.0 multiples of the median − see later) and the other becomes anaemic (MCA PSV >1.5 MoM) in the absence of significantly discordant liquor volumes. It is unclear at present how TAPS should be treated. Laser, or repeat laser ablation carries significant risks and is technically difficult. Intrauterine transfusion of the anaemic twin will result in an increase in the haemoglobin of the other, already polycythaemic, co-twin. The RCOG Green-Top Guideline 51 (management of monochorionic twin pregnancy) does not recommend routine screening for TAPS in all MCDA twin pregnancies, only those that are complicated, for example by selective fetal growth restriction, or those that have undergone laser ablation already for TTTS.

Death of a monochorionic twin in-utero from any cause may result in anaemia in the surviving twin. Death may occur before, or after, laser treatment for TTTS, or secondary to severe selective fetal growth restriction. As one twin dies, it is thought to vasodilate and certainly there will be cardiac pump failure. It is postulated that during the death, blood flows across the placental anastomoses from the previously healthier twin, potentially resulting in hypotension, hypovolaemia, ischaemia and anaemia in the co-twin. Survivors of a fetal monochorionic co-twin death should certainly be investigated for fetal anaemia and treated if the anaemia is severe.

Fetal infections

Although CMV, toxoplasmosis and syphilis have all been documented to cause fetal anaemia, Parvovirus B19 infections account for the vast majority of cases of fetal anaemia caused by infectious agents. This DNA virus causes a benign childhood coryzal illness known as erythema infectiosum, or 'slapped cheek syndrome'. Infected adults are often asymptomatic, although an arthropathy has been reported. Parvovirus has a propensity to infect red cell precursors in the bone marrow, temporarily shutting off erythropoiesis. This can cause an aplastic crisis in indivduals who are immunocompromised or who have an underlying haemolytic anaemia. Fetal red blood cells have a shorter life span than do adult red cells, meaning that the unborn baby may become very anaemic during the time that their bone marrow is rendered inactive by the virus. This anaemia, combined with a direct action of the virus on cardiac muscle and the liver, can cause fetal hydrops and death. However, the fetus may also recover spontaneously without need of rescue.

Approximately half of all pregnant women are already immune to parvovirus, having had an infection earlier in their life (which conveys subsequent lifelong immunity). Sharing a house with an infected individual carries more than a 50% risk of infection in the non-immune, and women who work with children are at a 1-in-3 risk of infection if there is a local outbreak in schools and nurseries. The incidence of parvovirus is cyclical, with a peak every 3−4 years in the UK. The vertical transmission risk is approximately 30%. Infections occurring <20 weeks' gestation carry the greatest risk of fetal loss (13%). Following maternal seroconversion (diagnosed by finding IgM antibodies in the serum of an exposed patient, or IgG in a woman who had no Parvovirus antibodies in her booking sample), surveillance for 10−12 weeks for fetal anaemia is recommended, with ultrasound

scans every 1–2 weeks. It can be extremely difficult to know whether anaemia secondary to parvovirus infection is worsening, and how severe it will become, or if it is resolving and therefore making treatment unnecessary. Fortunately, a single intrauterine blood transfusion is usually sufficient and in view of how poorly this may be tolerated by a hydropic fetus, the tendency is to treat fetal anaemia in this situation, rather than managing conservatively and risking the fetus becoming very unwell.

Fetal bone marrow disorders

Fetal bone marrow disorders are extremely rare but may cause fetal anaemia, neutropaenia and thrombocytopaenia. Fanconi anaemia is an autosomal recessive single gene disorder which has widespread implications in addition to bone marrow failure. The fetus may also have forearm or thumb anomalies, renal, genital and/or cardiac abnormalities. Prenatal diagnosis of this condition is made by culturing amniocytes in a particular way which results in chromosomal breakage in affected pregnancies. Diamond-Blackfan anaemia is caused by mutations in a variety of other single genes, and tends to be inherited in an autosomal dominant fashion. Clinically it overlaps significantly with Fanconi-anaemia. Uncommonly, a fetus with Trisomy 21 will develop anaemia and hydrops secondary to a transient myeloproliferative disorder caused by the combination of trisomy for the ERG gene found on chromosome 21, and a mutation in the GATA1 gene on the X chromosome.

Inherited red cell abnormalities

Haemoglobinopathies, red cell membrane defects and erythrocyte enzyme disorders can all cause fetal anaemia.

The haemoglobinopathies are disorders of haemoglobin production. Normal individuals have four working copies of the α-globin gene (αα/αα). Loss of one of these copies results in silent carrier status (-α/αα). Loss of two copies causes either cis (–/αα) or trans (-α/-α) α-thalassaemia trait. One working copy results in HbH disease (–/-α). If two cis α-thalassaemia carriers have a pregnancy together, there is a 1-in-4 risk of Hb Bart's (–/–) in the offspring. No functional α-globin chains are produced. The fetal γ-globin chains form tetramers γ_4 which have a very high affinity for oxygen and are poor at giving it up to peripheral tissues. The fetus becomes hypoxic, develops cardiac failure and hydrops, and will inevitably die without intervention. These α-globin mutations/deletions are most common in South-East Asia where large numbers of unborn babies are at risk of this condition. It is of course amenable to early prenatal diagnosis by CVS or amniocentesis in the pregnancies of known carriers. An increasing number of survivors of Hb Bart's disease are being reported, rescued by serial fetal blood transfusions. Antenatal intervention remains ethically challenging. Survivors require lifelong blood transfusions, or bone marrow transplantation at a very early stage of life. Major growth deficiencies, complications from iron overload and neurodevelopmental delay are common. Trials are underway of stem cell transplantation into the affected fetus.

Inherited red cell membrane disorders leading to rapid haemolysis may also rarely be the cause of fetal anaemia. Hereditary spherocytosis occurs as a result of a genetic defect in one of five genes coding for α-spectrin, β-spectrin, Ankyrin-1, band 3 or protein 4.2 and is mostly inherited as an autosomal dominant trait, although recessive patterns of inheritance have also been recorded. Red cell enzyme disorders, such as pyruvate kinase deficiency and G6PD deficiency, have also been implicated in rare cases of fetal anaemia. Pyruvate kinase is critical for glycolysis and ATP synthesis in red blood cells. Deficiency results in premature red cell destruction and subsequent anaemia.

Fetal and placental tumours

Chorioangiomas and sacrococcygeal tumours have been documented as causes of fetal anaemia, particularly large ones. Anaemia may occur as a result of haemorrhage into the tumour or consumption and destruction of the red cells within the tumour. Case reports attest to successful treatment of the fetal anaemia in such situations.

Diagnosis of fetal anaemia

Ultimately, the only truly diagnostic prenatal test for fetal anaemia is fetal blood sampling, a technically difficult investigation associated with a degree of risk. Some other form of screening for fetal anaemia is desirable to limit the number of fetal blood samplings required. Acute moderate to severe fetal anaemia caused by significant FMH over a short time period is likely to present with fetal compromise or fetal death, and the anaemia may only be diagnosed following birth. The chronic development of fetal anaemia however causes changes detectable on ultrasound and even the CTG in some cases. However, sinusoidal CTG patterns (see Figure 1) are rare, and often go unrecognised as a sign of fetal anaemia, and 'saw-tooth' or 'pseudosinusoidal' heart rate traces are common and misleading false positives. Consequently, the CTG is not suitable as a tool for surveillance or diagnosis of fetal anaemia. Fetal haemolytic disease results in elevated levels of bilirubin in the amniotic fluid. For many years, amniotic fluid bilirubin levels measured indirectly using spectrophotometry of serial amniocentesis samples were used as a surrogate marker for significant fetal anaemia. This invasive test was unpleasant, associated with risk and hampered by significant false positive and negative rates, and is of no value in the assessment of fetal anaemia resulting from non-haemolytic causes.

Hydropic changes in the fetus, including ascites, skin oedema, pleural and pericardial effusions, cardiomegaly, polyhydramnios and placentomegaly (see Figure 2) are non-specific signs of very severe chronic fetal anaemia which do not develop until fetal haemoglobin levels are critically low (typically less than 40 g/L). Treatment for anaemia in the hydropic fetus has poorer short-term and long-term outcomes (see later) and it is clear that these ultrasound features also are neither sensitive nor specific enough for the timely prediction of significant fetal anaemia.

Doppler ultrasound now provides the gold standard for screening and preliminary diagnosis of fetal anaemia of any cause. Blood in an anaemic fetus is less viscous and the velocity of blood flow in certain fetal vessels can be measured and be seen to be elevated above the normal range. Cardiac output may also be elevated somewhat in these fetuses, further contributing (although to a much lesser extent) to the increase in peak systolic blood flow velocities. A group led by Mari are usually credited for bringing the use of middle cerebral artery peak systolic velocity

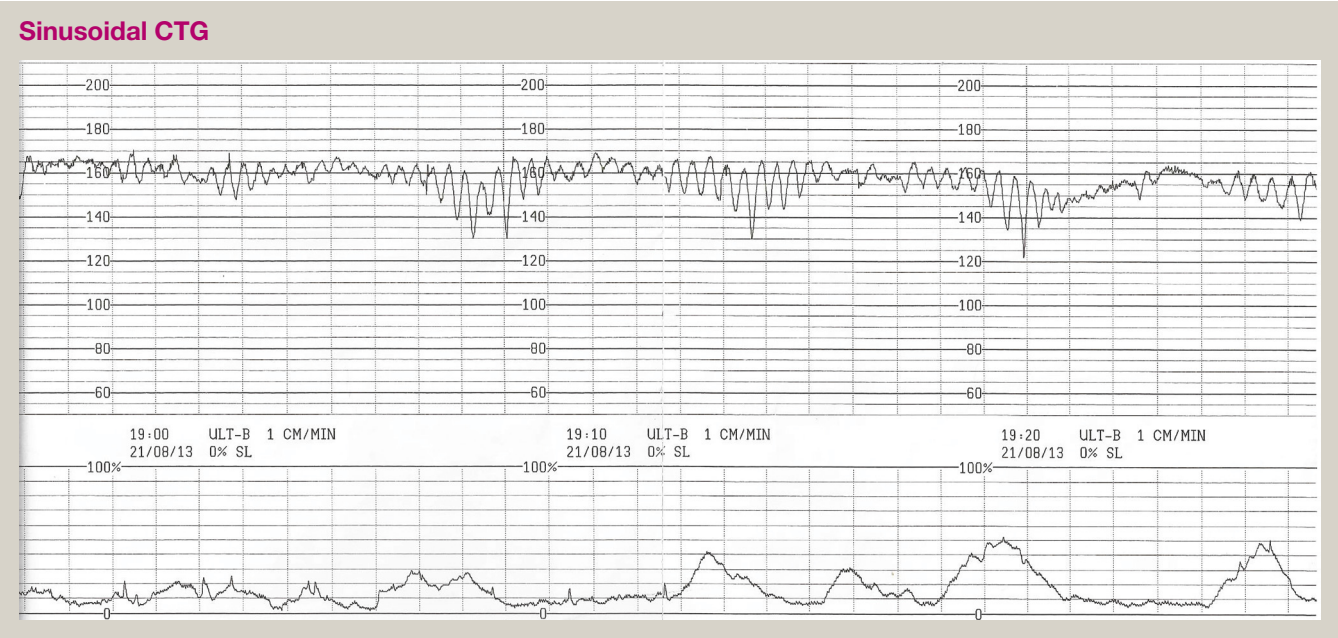

Figure 1

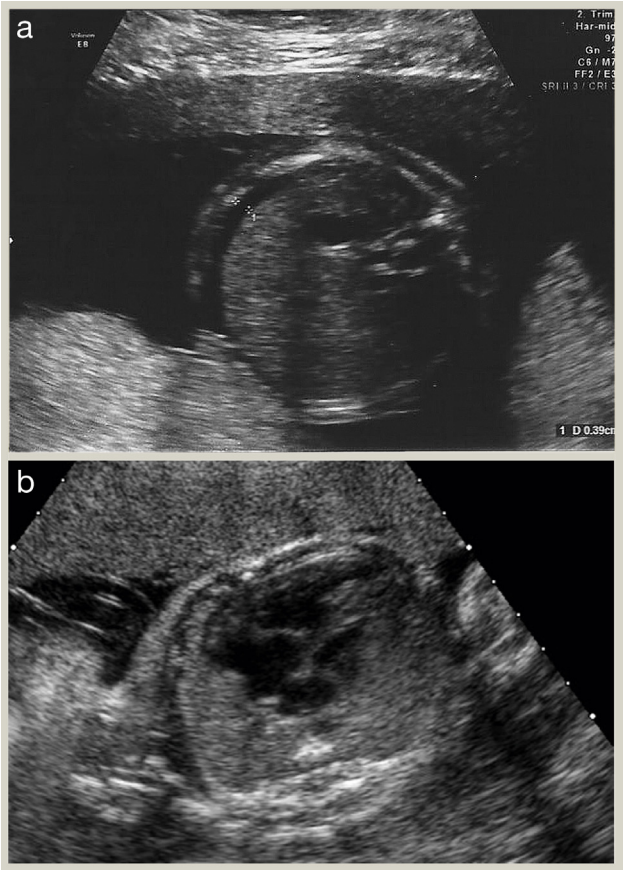

Figure 2 Ultrasound features of severe anaemia: (a) fetal ascites; (b) cardiomegaly and pericardial effusion.

(MCA PSV) measurements into widespread mainstream practice for the non-invasive assessment of fetal anaemia (Figure 3a). The middle cerebral artery is usually readily accessible for Doppler measurements, and the angle of correction means that absolute velocities can be recorded (unlike when assessing a growth restricted fetus when pulsatility index, i.e. a ratio, is used). The fetus must be quiescent, and a few measurements are usually made. The Doppler gate should be placed at the proximal part of the near field MCA, just as it emerges from the Circle of Willis. The value is plotted on a chart, and significant anaemia is highly unlikely with values which lie below 1.5 multiples of the median for the gestation in question (Figure 3b). As values exceed this threshold, the likelihood of significant fetal anaemia increases.

This is actually a screening test for fetal anaemia, and is not definitively diagnostic. False positives (12%) and negatives (uncommon) do occur, the former most commonly when the measurement is taken whilst the fetus is active. The overall accuracy has been quoted as 85%, which is 9% better than the use of serial amniocentesis and OD450 estimations for cases of red cell alloimmunisation, and also clearly avoids the risks associated with repeated invasive tests. When the MCA PSV is greater than 1.5 MoM, a fetal blood sampling should be performed if the values remain high on repeated testing and the fetus is deemed to be at risk of fetal anaemia.

Treatment of fetal anaemia

Intrauterine fetal blood transfusion (IUT) is a highly effective treatment for fetal anaemia however it requires highly specialised skills and is associated with a degree of risk. The use of IUT is well established for fetal alloimmune haemolytic anaemia and parvovirus infections, and it has also been used to treat anaemia caused by all the conditions already discussed. However, conservative management (e.g. in parvovirus or FMH), or placental laser (in TAPS), or earlier delivery (whatever the aetiology of the anaemia) should always at least be considered as alternatives to IUT. Use of human immunoglobulin and

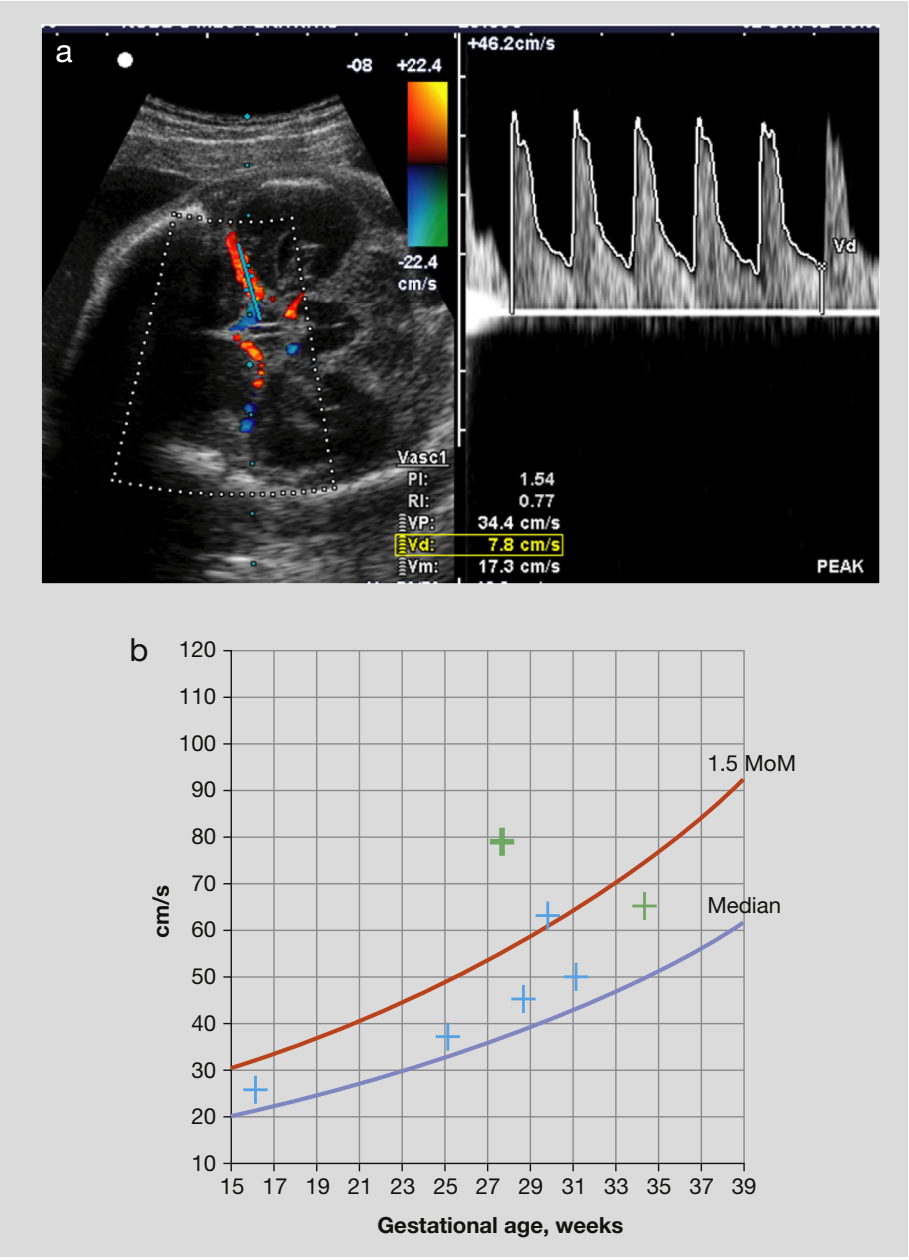

Figure 3 a: Measurement of the middle cerebral artery Doppler peak systolic velocity (MCA PSV).b. MCA PSV measurements taken from a Rhesus D isoimmunised pregnancy. The elevated MCA PSV levels at 28 and 30 weeks' gestation are followed by intrauterine transfusions which then bring down the peak systolic velocities into the normal range.

plasmapheresis have been frequently documented as adjunctive therapies for severe fetal haemolytic disease caused by red cell antibodies, although this strategy has not been exposed to randomised controlled trials as yet.

Pioneering fetal blood transfusions in the 1960s were performed into the fetal peritoneal cavity, and this remains a valid site for transfusion in cases of severe anaemia at very early gestations. Transfused red blood cells are absorbed across the gut lymphatics, although this can be impeded by fetal hydrops and, at best, takes some time to improve fetal haemoglobin levels. Intravascular IUTs into the umbilical vein at the placental cord insertion were later performed guided by fetoscopy (1981), and then by ultrasound as the quality of imaging improved. IUT into the intrahepatic portion of the hepatic vein under ultrasound guidance was described by Nicolini in 1990 and is particularly helpful if the placenta is posterior. These latter two sites have never been compared directly in a trial, and transfusion practitioners will usually choose their approach on a case-by-case basis. Transfusion into the umbilcal vein in a free loop of cord is less commonly practiced, and is associated with a greater risk of fetal heart rate abnormalities, including bradycardia. Direct intracardiac transfusions are usually reserved now for extremely early cases of fetal anaemia when all other routes have been ruled out. Some practitioners use paralytic agents such as

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 bradycardia/FHR abnormalities)
- Perinatal asphyxia
- Neonatal death
- Formation of new red cell antibodies
- Further stimulation of alloimmune antibody response

Table 4

vecuronium or rocuronium to limit the risk of needle dislodgement, and there is evidence supporting this strategy. Whichever fetal site is chosen for the IUT, maternal (and therefore fetal) sedation is usually prescribed. Under aseptic ultrasound guidance the needle is inserted into the vessel and a haemoglobin sample obtained and measured urgently with a bedside machine. A calculation is made using the current feto-placental volume (there are charts and on-line predictors for this based on gestation and/or estimated fetal weight), the level of anaemia and the haematocrit of the donated blood (which is usually very high to limit the volume required). The blood is then transfused without needing to reinsert the needle, usually in small aliquots over a period of time so as not to fluid overload the baby. If the fetus is hydropic then the total volume of blood transfused should be reduced, and given very slowly, and a second follow up transfusion given a few days later to reach the target haemoglobin over two procedures. Depending on the cause of anaemia, one transfusion may suffice (usually the case with parvovirus infections, for example), or serial IUTs may be required, for example in cases of alloimmune fetal haemolytic disease. Timing of subsequent transfusions may be based on MCA PSV measurements, although there is suggestion that these become less sensitive the more IUTs have been performed, perhaps due to the different properties of the transfused adult red blood cells. Transfusions will usually be required every two to three weeks in cases of red cell alloimmunisation and if the last is performed at 34–35 weeks' gestation delivery can then usually be safely deferred until 37–38 weeks' gestation.

The potential complications of IUT are listed in Table 4. 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.

The outcome of fetal anaemia and treatment with IUT is very much determined by the underlying cause, of course. Good quality data are only really available in red cell alloimmunisation. 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. ◆

FURTHER READING

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Practice points

- Fetal anaemia may develop acutely, or over a period of time, depending on the aetiology. The consequences for the fetus and newborn are critically dependent on the timing, rapidity of onset, and underlying cause of the anaemia
- Fetomaternal haemorrhage can be quantified using the Kleihauer test, or flow cytometry
- Fetal anaemia secondary to all causes can be screened for, and monitored, using middle artery peak systolic velocity measurements. Confirmation of fetal anaemia can only come from cordocentesis or newborn blood testing
- Some cases of fetal anaemia can be managed conservatively, or by earlier delivery. Intrauterine transfusion is a highly effective treatment for fetal anaemia developing at preterm gestations, but it requires subspecialist skills and is not always appropriate, depending on the cause