Identification and management of fetal anaemia: a practical guide

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Key content
• Fetal anaemia can be caused by alloimmune or infectious red cell destruction, disorders of fetal red cell production, fetal haemorrhage and as a complication of monochorionic multifetal pregnancy.
• A fetus at risk from maternal alloimmunisation can be detected by maternal serum screening for red cell antibodies and by fetal ultrasonography.
• Undiagnosed cases may present in routine obstetric practice, so awareness of the identification and initial management of fetal anaemia is important.
• Pregnancies must be triaged depending on clinical urgency, with input from fetal medicine specialists required.
• Developments in fetal ultrasound assessment and in fetal therapy have improved outcomes and contemporary research will focus on improving long term outcomes for neonatal survivors.

Learning objectives
• To understand the varied aetiologies and pathophysiology of fetal anaemia and to adopt a system for reaching a diagnosis.
• To appreciate the different diagnostic tools available, comprising ultrasonography, microbiological testing, noninvasive and invasive tests in fetal medicine units and electronic fetal monitoring in the acute setting.

Ethical issues
• Management involves balancing maternal and fetal risks.
• Research ethics should be considered in relation to experimental treatments and trials in fetal therapy.

Keywords: alloimmunisation / fetal anaemia / fetomaternal haemorrhage / in utero transfusion / middle cerebral artery Doppler

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Introduction
Fetal anaemia is an uncommon but potentially dangerous complication of pregnancy that can lead to considerable fetal or neonatal morbidity and mortality if unrecognised and untreated. Among the multiple causes of fetal anaemia, the commonest is antibody-mediated destruction of red blood cells via maternal alloimmunisation. Infection (most frequently with parvovirus B19) is the major nonimmune aetiology of fetal anaemia. Rarer causes include fetal haemorrhage (occult or revealed), fetal tumours (for example, placental chorioangioma) and complications of monochorionicity in multiple pregnancies. Fetal haemoglobin (fHb) values should increase with advancing gestation to a mean of 150 g/L at 40 weeks.1 Well-defined fHb nomograms define severe anaemia as greater than 70 g/L below the mean for gestation, or less than 0.55 multiples of the median.1,2 Reduced tissue perfusion and oxygenation in severe anaemia leads to end organ dysfunction, including brain injury, high-output cardiac failure and, ultimately, intrauterine fetal death. The ‘hydrops zone’ on the nomogram is gestation dependent, ranging from fHb <40 g/L at 18 weeks of gestation to fHb <80 g/L at term.3

This article provides an overview of the prospective identification and management of fetal anaemia, along with a tabulated reference guide to key aspects of screening, diagnosis and management of the main underlying aetiologies encountered in obstetric practice. Failure to recognise and appropriately manage suspected fetal anaemia can be devastating, thus we present a diagnostic approach to fetal anaemia encompassing core principles of general obstetric and fetal medicine care, involving
immunoprophylaxis was discovered in the 1960s. Now, was most frequently caused by anti-D antibody. Anti-D and ‘E’ antigens can cause severe HDFN. Historically, HDFN alloimmunisation caused by incompatibility with Rh ‘D’, ‘c’ and ‘E’ antigens can trigger alloimmunisation. Most clinically important in obstetrics; paternally inherited (autosomal dominant) antigens can trigger alloimmunisation. Alloimmunisation caused by incompatibility with Rh ‘D’, ‘c’ and ‘E’ antigens can cause severe HDFN. Historically, HDFN was most frequently caused by anti-D antibody. Anti-D immunoprophylaxis was discovered in the 1960s. Now, widespread use of anti-D immunoglobulin prenatally and immediately postnatally has dropped rates of D-alloimmunisation to 2%. Anti-E is now the most prevalent HDFN-causing alloantibody. The rarer ‘K’ and ‘k’ antigens of the Kell group can cause severe, early-onset anaemia at lower levels because they suppress erythropoiesis, as well as causing red cell destruction. Other antibody groups capable of causing HDFN (more commonly neonatal jaundice) include the Fy, Jk and MNS systems. The most clinically important red cell antigens are listed in Table 1.

About 15% of white European and 5% of African and Indian ancestral groups lack the D antigen (Rh-negative) on their RBCs. East Asian women are almost always Rh-positive. The first IgM alloantibody response cannot cross the placenta. However, on re-exposure to the antigen, the ‘secondary’ IgG response is more pronounced so the antibodies can cross the placenta, potentially causing fetal anaemia. Given that IgG responses are characteristically mounted over several months, clinically significant alloimmune effects that may pose a risk to the fetus are more likely in a subsequent, rather than index, pregnancy. IgG transport across the placenta is mediated by the neonatal Fc receptor (FcRn). In the fetal circulation, IgG alloantibodies target RBCs, or their progenitors, for destruction. Fetal anaemia results from suppression of erythropoiesis or by haemolysis.

The Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guideline on the management of women with red cell antibodies during pregnancy provides clinicians with evidence-based recommendations for antenatal screening, diagnosis and management of alloimmunised pregnancies. Maternal ABO and D blood group and alloantibody status should be ascertained at booking and checked again at 28 weeks of gestation. Pregnancies with a high chance of HDFN include those in women with a previous history of a fetus or newborn affected with haemolytic disease, or who have a critical level of high-risk alloantibody (Table 2). Such women should receive preconceptual counselling and be referred to a fetal medicine specialist.

The advent of cell-free fetal DNA (cffDNA) testing from maternal blood allows noninvasive identification of fetal RBC antigens, including D, c, C, e, E and Kell. The sensitivity

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**Box 1. Sensitising events for Rh D-negative women in pregnancy**

- Ectopic pregnancy
- Early miscarriage complicated by pain and/or excessive bleeding
- Uterine evacuation (miscarriage, molar pregnancy, termination of pregnancy)
- Any pregnancy loss after 12 weeks (miscarriage and intrauterine death/stillbirth)
- Invasive fetal tests (amniocentesis, chorionic villus sampling, cordocentesis)
- Fetal therapy (transfusion, surgery, shunt insertion, laser, fetal reduction)
- External cephalic version
- Abdominal trauma
- Delivery, regardless of mode
- Intraoperative cell salvage

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| Condition                                      | Specific management guidance                                                                                                                                                                                                 |
|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Red cell alloimmunisation                     | **Ask:**                                                                                                                                                                                                                     |
|                                               | - Previous baby requiring transfusion or known HDFN                                                                                                                                                                          |
|                                               | **Test:**                                                                                                                                                                                                                   |
|                                               | - Maternal blood group and antibody status                                                                                                                                                                                  |
|                                               | - Fetal and paternal genotyping                                                                                                                                                                                            |
|                                               | **Refer to fetal medicine specialist:**                                                                                                                                                                                     |
|                                               | - Prior HDFN                                                                                                                                                                                                                  |
|                                               | - Ultrasound evidence of fetal anaemia (MCA-PSV or hydrops)                                                                                                                                                                |
|                                               | - Rapid rise in alloantibody or specific thresholds reached:                                                                                                                                                                 |
|                                               |   - Anti-D > 4 IU/ml (>15 likely severe)                                                                                                           |
|                                               |   - Anti-c > 7.5 IU/ml (>20 likely severe, lower threshold if co-existent anti-E)                                                                                   |
|                                               |   - Anti-K as soon as detected                                                                                                                                                                                                |
|                                               |   - Any other alloantibody titre ≥32                                                                                                                                                                                     |
|                                               | **Specifics:**                                                                                                                                                                                                                 |
|                                               |   - If maternal transfusion likely, need regular crossmatch sample                                                                                                                                                          |
| Fetal infection                                | **Ask:**                                                                                                                                                                                                                   |
|                                               |   - Current rash or febrile illness, onset                                                                                                                                                                                  |
|                                               |   - Unwell contacts and time of exposure (face-to-face or 15 minutes in same room is significant)                                                                                                                              |
|                                               | **Test:**                                                                                                                                                                                                                   |
|                                               |   - No routine screening                                                                                                                                                                                                     |
|                                               |   - Booking sera for IgG to determine seroconversion since                                                                                                                                                                  |
|                                               |   - Current blood sample (for symptomatic or asymptomatic women with contact); retest one month after contact if no IgG or IgM at initial test                                                                                     |
|                                               |   - Consider amniocentesis or fetal blood sample to detect viral DNA                                                                                                                                                         |
|                                               | **Specifics:**                                                                                                                                                                                                                  |
|                                               |   - Serial ultrasound scanning from 4 weeks after symptom onset                                                                                                                                                               |
|                                               |   - Parvovirus B19: IgM present in maternal blood from first day after rash onset; no IgM means no infection in last 4 weeks; test saved booking blood for viral DNA load or IgG seroconversion or repeat sample for change in IgM reactivity; scan fetus weekly from 4–10 weeks after confirmed maternal infection; maternal infection after 24 weeks usually harmless |
|                                               |   - CMV: If maternal CMV IgG and IgM are positive, and IgG avidity low, infection is highly likely to have been within 3 months; antiviral drugs may be beneficial in congenital CMV                                                                 |
|                                               |   - Termination of pregnancy may be considered                                                                                                                                                                                |
| Genetic and metabolic conditions               | **Ask:**                                                                                                                                                                                                                   |
|                                               |   - Family origin questionnaire (screening for haemoglobinopathy)                                                                                                                                                             |
|                                               | **Test:**                                                                                                                                                                                                                   |
|                                               |   - Haemoglobin electrophoresis                                                                                                                                                                                               |
|                                               |   - Parental DNA                                                                                                                                                                                                                 |
|                                               |   - Red cell enzyme assays (pyruvate kinase, G6PD)                                                                                                                                                                             |
|                                               |   - Invasive test for genetic diagnosis                                                                                                                                                                                     |
| Vascular tumours                               | **Specifics:**                                                                                                                                                                                                                 |
|                                               |   - Regular Doppler assessment to screen for signs of high output state associated with fetal exsanguination                                                                                                                      |
|                                               |   - MRI                                                                                                                                                                                                                       |
|                                               |   - Laser coagulation or radiofrequency ablation of tumour vessels                                                                                                                                                           |
|                                               |   - Open maternal fetal surgery for resection of SCT in selected, very preterm cases                                                                                                                                                   |
|                                               |   - Amniodrainage if severe polyhydramnios                                                                                                                                                                                    |
|                                               |   - Neonatal team to prepare for microangiopathic haemolytic anaemia and thrombocytopenia                                                                                                                                   |
| Vasa praevia                                   | **Specifics:**                                                                                                                                                                                                                 |
|                                               |   - Transvaginal colour Doppler ultrasound and rescans to confirm at 32 weeks                                                                                                                                                |
|                                               |   - Palpate for pulsating fetal vessels in the membranes on vaginal examination                                                                                                                                             |
|                                               |   - Consider inpatient management if preterm labour likely or antenatal bleeding                                                                                                                                           |
|                                               |   - Delivery 34–36 weeks after steroids                                                                                                                                                                                       |
Fetal anaemia

Table 2. (Continued)

| Condition | Specific management guidance |
|-----------|-------------------------------|
| Complications of monochorionicity | • Fortnightly scans in local unit from 16 weeks of gestation for all multifetal pregnancies with shared placenta |
|  | • Refer monochorionic multifetal pregnancies to a tertiary Fetal medicine centre if: |
|  | - Hydrops |
|  | - Cardiac dysfunction |
|  | - Unexplained polyhydramnios |
|  | - Abnormal umbilical artery Doppler velocimetry |
|  | - Single twin death |
|  | (These fetuses need Doppler assessment of MCA-PSV to detect TAPS) |
|  | • Weekly ultrasound surveillance using MCA-PSV after fetoscopic laser ablation for fetofetal transfusion syndrome and in selective fetal growth restriction (estimated fetal weight discordance ≥25% and an EFW <10th centile) |
|  | • Assess neuroanatomy of co-twin survivor(s) with ultrasound and later with MRI |
|  | • Fetoscopic laser ablation before 26 weeks, and after 26 weeks IUT for anaemia and exchange transfusion to dilute the polycythaemic circulation with Hartmann’s solution can be considered |

Abbreviations: CMV = cytomegalovirus; EFW = estimated fetal weight; G6PD = glucose-6-phosphate dehydrogenase; HDFN = haemolytic disease of the fetus and newborn; IgG = immunoglobulin G; IgM = immunoglobulin M; IU = international unit; IUT = intrauterine transfusion; MCA-PSV = middle cerebral artery peak systolic velocity; MRI = magnetic resonance imaging; SCT = sacrococcygeal teratoma; TAPS = twin anaemia polycythaemia sequence

and specificity of cffDNA RhD genotyping is almost 100%, so it can be considered a diagnostic test when used in this context. Rhesus D, c, C and e are detectable from 16 weeks of gestation and Kell from 20 weeks. Routine cffDNA-based testing reduces unnecessary anti-D administration and can be cost effective. Clinicians should be aware of the small risk of false negative ‘diagnosis’ and, if high-risk alloantibody level increases, then serial ultrasound surveillance should be considered, as for a sensitised pregnancy. Determination of paternal RBC antigen status and zygosity may be considered and, very rarely, invasive testing (chorionic villus sampling or amniocentesis) remains necessary for diagnostic certainty (if the father is heterozygous).

Alloimmunised women require blood tests every 4 weeks up to 28 weeks of gestation and fortnightly thereafter. Absolute levels of alloantibody (see Table 2), or a rapid rise in level (doubling over a 14-day period), are important. Levels and titres are less informative in a second at-risk pregnancy, when earlier referral is required. With Kell alloimmunisation, there is a lower threshold for specialist input because these alloantibodies can cause severe and unpredictable fetal anaemia (caused by suppressed erythropoiesis) irrespective of antibody levels and previous pregnancy outcome. Follow-up testing for lower risk alloantibodies is individualised.

Where available, routine use of RhD immune globulin has reduced the rate of red cell alloimmunisation, with developed countries following established protocols for immunoprophylaxis with anti-D IgG. An additional dose of anti-D is required within 72 hours of a recognised sensitising event where there is possible fetomaternal haemorrhage (Box 1). Adequate dosing (500 IU injection of anti-D is sufficient to cover 4 ml of fetal RBCs) is confirmed with the Kleihauer–Betke test, or with flow cytometry if the sensitising event occurs after 20 weeks of gestation.

Fetal infection

Anaemia can be the result of fetal viral infection following vertical transmission from a symptomatic or asymptomatic woman. The gestational age of infection and previous infections or exposure should be considered when assessing fetal risk. Human parvovirus B19 is probably the most common cause for viral-related fetal anaemia in the UK. It is a single-stranded DNA virus usually transmitted via respiratory droplets. In children, viraemia is usually heralded by flu-like illness, then manifests as a rash spreading from the face (‘slapped cheek syndrome’) to affect the trunk and limbs – possibly with arthralgia. Infections occurring in adulthood tend to be asymptomatic, although more severe disease, including aplastic crises, can occur in people who are immunocompromised. More than half of pregnant women will be immune because of infection before pregnancy, but in those without such immunity, an infection in the first half of pregnancy can cause fetal anaemia and hydrops secondary to viral destruction of fetal erythroid progenitor cells. The risk of fetal loss is estimated to be 13% with parvovirus B19 infection before 20 weeks of gestation and 0.5% with infection occurring later in pregnancy. There is no preventive strategy or licensed vaccine available for parvovirus. Most women infected give a clear history of exposure to a child with the acute viral illness. Useful guidance is available from Public Health England, with
pregnant women advised to notify a clinician promptly of any contact with, or development of, rash and to avoid exposing other pregnant women.20

Cytomegalovirus (CMV) is another important maternal infection that can cause fetal anaemia. Avidity is an important property in testing, with the strength of the IgG and antigen complex gradually increasing with time after primary infection, thus indicating the latency of infection. Low avidity is suggestive of recent infection.21 Approximately 2% of cases are associated with reactivation after a previous primary infection. This is helpful to identify the timing of the primary infection and to stratify risk to the fetus. Rarer infective causes of fetal anaemia include toxoplasmosis, syphilis, malaria, rubella and herpes. Apart from fetal hydrops, there may be other ultrasound signs of congenital infection, including echogenic bowel, hepatic calcifications, organomegaly, a suspicion of dysplastic kidneys (often with accompanying oligohydramnios), ventriculomegaly and fetal growth restriction. Myocarditis and hepatitis may be important sequelae of vertical transmission of viral infection.

Detailed descriptions of the investigations and management of viral conditions in pregnancy are outside the scope of this article, but Table 2 outlines a basic approach. Further information can be found in the National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summary (for parvovirus)22 and the RCOG Scientific Impact Paper (for CMV).23

Disorders of erythropoiesis

Fetal anaemia can result from problems at any stage of red cell production in the bone marrow. It can be stage to inherited anaemias, metabolic syndromes or bone marrow failure. Aplastic anaemia can result from toxicity of drugs or radiation, or an underlying genetic problem. Alpha-thalassaemia, predominantly in couples of Mediterranean and Asian origin, is the commonest type of inherited anaemia, in which the alpha-globin chains in haemoglobin are reduced or absent. Less normal haemoglobin results in less oxygen delivery to fetal tissues. A fetus born to two parents with alpha-thalassaemia trait has a one in four chance of having alpha-thalassaemia major. In this condition, the complete lack of normal haemoglobin leads to the so-called Barts hydrops fetalis, which can be ‘mirrored’ by maternal pre-eclampsia and is associated with antepartum haemorrhage.24 A markedly thickened placenta is a classic sonographic sign.

Genetic disorders of red cell production include congenital erythropoietic porphyria, Fanconi anaemia and Diamond–Blackfan anaemia. Transient abnormal myelopoiesis (TAM) has a particular association with trisomy 21.25 Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked, haemolytic anaemia, which is commonest in African ancestral groups. In G6PD deficiency, red cells are less tolerant to oxidative stress, which becomes apparent in the context of infection, maternal fava bean ingestion or drug toxicity.26 Pyruvate kinase and glucose phosphate isomerase deficiencies also cause fetal anaemia.

Vascular tumours

Any tumour of the fetus or placenta that sequesters red blood cells can cause fetal anaemia. Sacrococcygeal teratoma (SCT) is the commonest fetal tumour, in which red cells can be consumed or damaged as they pass through, or there can be bleeding within the tumour leading to fetal anaemia. A large cohort study27 found that 9.1% of fetuses with SCT developed hydrops, although such ultrasound findings with tumours may be attributed to high output cardiac failure rather than to anaemia. A ‘giant’ placental chorioangioma, seen on ultrasound with colour Doppler as a ‘mass’ protruding into the amniotic cavity from the placenta with high vascularity, may cause a hyperdynamic circulation with associated polyhydramnios. Fetal anaemia results from sequestration and destruction of fetal RBCs within the thrombosed vascular mass of the tumour.28 Other tumours, including haemangiomata (for example, in the fetal liver) and arteriovenous malformations can similarly cause fetal anaemia.

Fetomaternal haemorrhage (transplacental haemorrhage)

Any antepartum haemorrhage can cause loss of fetal red blood cells into the maternal circulation. A woman may present without overt clinical signs of bleeding, and reduced fetal movements may be the only clue. Fetomaternal haemorrhage (FMH) can be detected by the Kleihauer–Betke test, or by flow cytometry.7 The effect on the fetus depends on gestation (because considerable volume expansion occurs in the fetus and placenta throughout pregnancy) and timescale, with a gradually evolving chronic anaemia being better tolerated. In pregnancies with recurrent FMH remote from term, without acute maternal or fetal compromise, supportive care with ultrasound surveillance can be offered; however, the outlook is unpredictable and these cases require caution.

A sudden large bleed, as in a massive placental abruption or ruptured vasa praevia, will cause fetal hypotension, acidemia and eventually death. Placental abruption is an obstetric emergency, usually occurring without warning and mostly in low-risk pregnancies without modifiable risk factors.29 Other causes of FMH are listed in Box 1. Guidance for the management of antepartum haemorrhage is provided by the RCOG.29
Vasa praevia

A diagnosis of vasa praevia may be made following painless vaginal bleeding coinciding with membrane rupture and fetal compromise. In such cases, there is no time for diagnostic testing because of associated 'fetal distress' requiring urgent delivery to prevent fetal demise. Routine antenatal screening does not currently occur in the UK for this condition, but if discovered in an asymptomatic woman, then RCOG guidelines support delivery by caesarean section at 34–36 weeks of gestation, after ultrasound confirmation of persistence and administration of steroids for fetal lung maturity. In situations of anterior placenta praevia, the placenta may need to be transected during a caesarean section to facilitate delivery, in which case immediate cord clamping is required to minimise fetal blood loss. In any case of major antepartum haemorrhage, neonatal support should be available at delivery. A longer length of cord should be left attached to the newborn to facilitate umbilical artery catheterisation in case transfusion is required.

Complications of monochorionicity in multifetal pregnancies

Fetal anaemia can be a consequence of vascular anastomoses connecting the fetal circulations in multiple pregnancies with a shared placenta. Specific complications of monochorionicity are subacute/chronic fetal anaemia associated with twin anaemia polycythaemia sequence (TAPS) and acute anaemia in the surviving fetus following co-twin demise. TAPS is defined by a significant discordance in haemoglobin levels between twins, without substantial differences in amniotic fluid volume. Prenatal prediction relies on ultrasound Doppler imaging of the middle cerebral artery peak systolic velocity (MCA-PSV, described in the next section). TAPS arises from a chronic transfusion of blood from a donor to recipient fetus via miniscule (<1 mm) artery–vein anastomoses. It spontaneously affects up to 5% of all monochorionic diamniotic pregnancies. After fetoscopic laser ablation for fetofetal transfusion syndrome, TAPS has been reported in up to 16% of monochorionic twins. It is associated with incomplete ablation of placental anastomoses, although the Solomon technique can reduce the incidence of this complication to 3%. Single intrauterine fetal death complicates 1–2% of monochorionic twin pregnancies. Following this event, an acute transfusion from the surviving co-twin to the demised twin can occur, leading to anaemia, with the surviving co-twin being at significant risk of subsequent brain injury and death. Complexities surrounding the management of such cases mean that input from a tertiary fetal medicine centre is recommended; however, in the UK, this is not routinely screened for in uncomplicated monochorionic twins.

Principles of management of fetal anaemia

Identifying an anaemic fetus

Pregnancies at high risk of fetal anaemia can be identified antenatally from the booking history, routine screening to detect maternal serum antibodies at 12 and 28 weeks of gestation, ultrasonographic evidence of hydrops fetalis, or a high-risk fetal condition. Parous women should be asked at booking about prior transfusion history and previous fetal or neonatal transfusion. A history of neonatal jaundice should be sought. Maternal reporting of relevant infectious exposure or possible fetomaternal haemorrhage is more variable, but should also alert a clinician to evaluate for risk of fetal anaemia. High-risk cases should then be evaluated early by a fetal medicine specialist.

Direct fetal blood sampling is the ‘gold standard’ for the diagnosis of fetal anaemia, but carries a procedure-related risk of miscarriage or preterm birth of up to 2%. Increased cardiac output and reduced blood viscosity means that arterial blood flow in the brain of an anaemic fetus is increased. Doppler ultrasound assessment of the fetal MCA-PSV is used to screen for fetal anaemia (Figure 1). The ‘action line’ and consideration of fetal blood sampling is required at 1.5 multiples of the median MCA-PSV for gestational age. Extramedullary haematoopoiesis in a severely anaemic fetus causes hepatosplenomegaly, with subsequent liver congestion and impaired synthetic function, leading to extracellular fluid accumulation. Effusions, ascites, oedema and polyhydramnios can be detected by ultrasound in hydrops fetalis, defined as abnormal fetal fluid collections in two or more compartments. Outcomes are worse if hydrops is present, which makes early detection important. Ultrasound evidence of cardiac decompensation may include cardiomegaly and tricuspid regurgitation. When nonimmune hydrops is detected on ultrasound scan, maternal wellbeing should be assured, including assessment of blood pressure and dipstick urinalysis to exclude the maternal pre-eclampsia-like ‘mirror syndrome’.

Recently, magnetic resonance imaging (MRI) estimation of fetal haematocrit has been proposed as a more specific imaging technique to identify fetal anaemia (93% versus 88% for ultrasound MCA-PSV). However, this is a more expensive imaging resource, has not been shown to be cost effective and is not readily delivered by the bedside. While MRI is a less available resource, it may avoid unnecessary intervention at later gestations, or after fetal therapy where MCA-PSV is less specific. MRI can also provide additional information about the effect of severe anaemia on the fetal brain.
the first objective sign of anaemia or sudden fetomaternal haemorrhage and should trigger urgent senior review for consideration of imminent delivery.

**Intrauterine transfusion**

The first intrauterine transfusion (IUT) occurred in 1963 and is now performed as an ultrasound-guided percutaneous needle (usually 20–22G) procedure.\(^49,50\) Vascular access is commonly via the umbilical vein (at the placental cord root or intrahepatic vein, the latter with lower complication rates).\(^51,52\) Umbilical cord ‘free loops’ may be used. In obese women, or at earlier gestations (usually <20 weeks) when intravascular transfusion is technically challenging, intracardiac transfusion may be performed.\(^53\) In modern fetal medicine, intraperitoneal fetal transfusion is used to manage fetal anaemia (in a nonhydropic baby) usually prior to 20 weeks of gestation, often in combination with maternal intravenous immunoglobulin (IVIg) therapy in severely alloimmunised women.\(^54\) The evidence base most strongly supports in utero transfusion for alloimmune anaemia and parvovirus B19 infection, but it can also be used in selected cases of inherited anaemias.\(^52\) In a case series from the Dutch fetal therapy centre in Leiden,\(^55\) alloimmunisation accounted for 86% of IUTs, with the next commonest indications being parvovirus B19 (9%), TAPS (3.6%) and FMH (1.3%).

More than one in five women (with red cell alloimmunisation) undergoing IUT form additional alloantibodies, which may complicate future pregnancies.\(^56\) Precautions to decrease this complication include extended phenotype matching (Rhesus, K, Duffy, Kidd and S), use of a single, well-matched donor, or serial maternal blood donations for IUT.\(^56,57\) The presence of adult haemoglobin (from transfused packed cells) in the fetal circulation affects blood viscosity and MCA-PSV becomes a less specific screening test for fetal anaemia after IUT. Therefore, the timing of second and subsequent IUTs relies on use of MCA-PSV and the calculated fall of fetal Hb with time.\(^58\) The use of measured reticulocyte count in pre-transfusion fetal blood samples may give useful information and aid timing of further IUTs. In anaemia caused by RBC antibodies, the fetal reticulocyte count falls with subsequent transfusions and is an indirect marker of suppression of the endogenous erythropoiesis by the presence of a high proportion of donor-packed cells.\(^59\) This suppression is evidence that the proportion of circulating fetal RBCs are predominantly transfused cells and may aid the decision to space out the transfusions. In fetuses infected with human parvovirus B19, the fetal reticulocyte count at initial fetal blood sample provides an indication as to whether the endogenous erythropoiesis is recovering after infection. A reticulocyte count of greater than 10% can suggest recovering endogenous red cell production, thus allowing a more conservative approach to management. Parvovirus B19 is usually associated with pancytopenia and, if significant thrombocytopenia is observed, then a platelet transfusion is also required. If the fetal haemoglobin is <4 g/L, clinicians must take caution not to over-transfuse the fetus because increases in circulating volume and haematocrit can adversely affect fetal haemodynamics, and a significant number of fetuses have associated parvovirus myocarditis.\(^60\) Fetal and neonatal top-up transfusions are made more likely by additional antibody formation after transfusion and the suppression of fetal erythropoiesis, with a recent study showing that 88% of neonates required further intervention.\(^51\)

The risk of harm to the fetus from IUT is 1–3%; intervention at earlier gestations (<20 weeks) is more hazardous because fetal vessels are smaller.\(^62\) Intrauterine infection (0.1% per transfusion)\(^52\) and ruptured membranes (1.4%)\(^51\) may complicate transfusions and lead to iatrogenic preterm birth.\(^63\)

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**Figure 1.** Middle cerebral artery Doppler assessment. This ultrasound image shows an axial section of the fetal head, with Doppler insonation of the fetal middle cerebral artery, close to its origin from the internal carotid artery in the Circle of Willis. The peak systolic velocity is measured, using angle correction and in the absence of fetal breathing movements.

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but procedure-related preterm birth has been reduced to as low as 0.1% per procedure in a high volume centre.\textsuperscript{52} In the largest series of 1678 IUTs in 589 fetuses, the procedure-related complication rate was 3.3% and the perinatal mortality rate 1.8%.\textsuperscript{52} An overall 84% survival rate following IUT has been reported, with greater than 90% survival in the absence of hydrops.\textsuperscript{64,65}

Timing of delivery depends on local protocols and the cause of anaemia. Fetal therapy is unlikely to be offered after 34 weeks of gestation. Term vaginal birth is possible in the absence of fetal compromise, with induction of labour likely to be recommended at 37 weeks of gestation if the pregnancy continues.\textsuperscript{12,66} Iatrogenic prematurity and the need for neonatal transfusion or prolonged phototherapy must be borne in mind.

**Medical treatments**

Intravenous immunoglobulins (IV Ig) given at high doses may block the transport of alloantibodies across the placenta by competitive inhibition.\textsuperscript{12} IV Ig can reduce maternal alloantibody production and delay clinically significant anaemia until IUT is more feasible.\textsuperscript{54,67} The Postponing Early intrauterine Transfusion with Intravenous immunoglobulin Treatment (PETIT) study\textsuperscript{68} investigated the outcomes of pregnancies in women with prior alloimmunised pregnancy complicated by severe fetal anaemia. IV Ig therapy (24 women) delayed the onset of clinically significant anaemia compared with the index pregnancy (by 15 days) and compared with the group not treated with IV Ig (28 women, by 9 days). This prolongation is insufficient to make a clinically useful reduction in the risk of invasive fetal therapy. Maternal IV Ig therapy was associated with reduction in hydrops and neonatal exchange transfusion, especially when initiated early. Overall survival was 88%, with no difference between groups.

Maternal plasma exchange can clear alloantibodies from the maternal circulation. It can be beneficial when a previous pregnancy has been severely affected by fetal anaemia, or if large quantities of Rh-positive red blood cells need to be cleared from a Rh-negative patient acutely. Potential adverse effects relate to maternal morbidity (for example, infection, haematoma formation) and altered maternal and fetal haemodynamics, as well as the loss of systemically important proteins.\textsuperscript{69}

Immunomodulatory therapies may prevent alloimmunisation in high-risk women prior to RBC antigen exposure, but current evidence is limited to case series, with azathioprine, promethazine and prednisolone amongst the candidate drugs.\textsuperscript{70} A clinical study of M281 (nipocalimab, Momenta\textsuperscript{80} Pharmaceuticals), a monoclonal antibody that blocks transplacental IgG transfer, is investigating whether it can attenuate the risks of alloimmune fetal anaemia and prolong the gestation when IUT may be required.\textsuperscript{71}

**Outcomes of fetal anaemia**

Red cell alloimmunisation causes over 50 000 stillbirths per year worldwide.\textsuperscript{72} Countries with comprehensive antenatal care have reduced the prevalence of HDFN to 2.5/100 000 live births.\textsuperscript{72} Many units now prolong affected pregnancies until 37 weeks of gestation (if safe) to reduce iatrogenic preterm birth and caesarean section rates, with their associated morbidity.\textsuperscript{73} For babies with antenatally diagnosed anaemia, deferred cord clamping at the time of delivery has been shown to reduce the need for neonatal exchange or top-up transfusion.\textsuperscript{74} Cord blood of at-risk babies is screened for HDFN by performing a direct agglutinin test, with haemoglobin and bilirubin checked after a positive screen to make the diagnosis.

Maternal antibodies remain in a baby’s circulation for up to 6 months. Continuing red cell destruction can lead to chronic unconjugated hyperbilirubinaemia and brain injury (kernicterus). Neonatal jaundice is treated with phototherapy or exchange transfusion.\textsuperscript{75} Cholestatic jaundice (conjugated hyperbilirubinaemia) complicates the postnatal course of 13% of HDFN cases and is associated with IUT and RhD alloimmunisation.\textsuperscript{76}

Early neonatal anaemia in HDFN (within 7 days) is determined by in utero events and late anaemia is divided into hyporegenerative and haemolytic aetiologies.\textsuperscript{77} Top-up transfusions occur in up to four out of five neonates with HDFN until late postpartum anaemia resolves.\textsuperscript{75} Multiply transfused babies are potentially at risk of iron overload. In a systematic review of nine single-centre studies of outcomes in children born after IUT, the pooled rate of cerebral palsy was 2.4% (13/549).\textsuperscript{78} The LOTUS study followed up 291 children at a median age of 8.2 years following IUT for alloimmune fetal anaemia and found neurodevelopmental impairment in 4.8%.\textsuperscript{79} After TAPS, the donor twin is at increased risk of neurodevelopmental impairment (four-fold higher than the recipient) and the incidence of cognitive delay and deafness is increased, warranting long term follow-up.\textsuperscript{80} ABO incompatibility is a neonatal, rather than fetal, problem; parents can be reassured that this mild haemolytic anaemia does not get worse in successive pregnancies.

**Conclusion**

Fetal anaemia is an important condition, of which clinicians of all levels should be aware. Appropriate antenatal screening and identification of pregnancies at high risk of fetal anaemia will aid prompt diagnosis. Use of ultrasound and Doppler investigation of MCA-PSV and referral to fetal medicine specialists for assessment and therapy has been shown to improve outcomes.
Disclosure of interests
There are no conflicts of interests.

Contribution to authorship
JC and LG researched and wrote the article. MK reviewed and edited the article. RKM instigated and edited the article. All authors approved the final version.

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