Fetal anaemia

Alec McEwan

Abstract

Fetal anaemia is a rare condition which can result from a failure of production of fetal red blood cells, accelerated haemolysis, or fetal bleeding. The three most common causes are parvovirus B19 infection, red cell isoimmunisation and fetomaternal haemorrhage. All obstetricians are likely to encounter these clinical scenarios at some point, even if management is predominantly by fetal medicine specialists. All three topics have been covered in previous articles of this journal, but here are presented three real cases illustrating these causes of fetal anaemia, and emphasising again the key points.

Keywords anti-D antibodies; fetal anaemia; fetomaternal haemorrhage; hydrops; Kleihauer; middle cerebral artery peak systolic velocity; parvovirus B19; red cell isoimmunisation

Introduction

Fetal anaemia is a relatively rare recurrence, usually managed by fetal medicine specialists and neonatologists. Red cell alloimmunisation is one of the most common causes, and this topic was covered in detail in Volume 20 of this journal (issue 2). This article describes three case histories which illustrate the causes and presentations of fetal anaemia and emphasises the need for all obstetricians to have knowledge of this uncommon condition.

Anaemia develops when red cell production is inadequate, or when breakdown of erythrocytes is accelerated, or when red cells are lost through bleeding. All three mechanisms can also be seen to cause anaemia in the fetus (Table 1).

Diagnosing anaemia in a child or adult is simple to do by measuring haemoglobin values on venous blood. Red cell size and haemoglobin concentration, and a blood film, go a long way towards isolating a cause when combined with the full clinical picture. Fetal blood sampling is possible, but very much more technically challenging and hazardous, requiring specialist skills only found in a few tertiary fetal medicine centres. Under ultrasound guidance, a 20 gauge needle is inserted into the umbilical vein either at the placental cord insertion, or as it passes through the fetal liver, and 1 ml of blood aspirated for testing. The risks of fetal bradycardia and bleeding, and membrane rupture or chorioamnionitis are quoted at approximately 1–2% per sampling, not to mention the possibility of failure. For many years, amniocentesis and spectrophotometric measurement of liquor bilirubin was used as a surrogate for fetal anaemia in haemolytic conditions (mostly Rhesus D isoimmunisation). Although easier to perform than fetal blood sampling, it still carried risk, and also was known to have a significant false positive and negative rate. Non-invasive methods of testing for fetal anaemia using the CTG (see cases 1 and 2) and ultrasound scanning for fetal hydrops (see case 2 and 3) are also highly insensitive, with hydrops only occurring when the fetal haemoglobin is life threateningly low, and usually only when the development of the fetal anaemia has occurred over a prolonged time frame i.e. not with acute fetal bleeding.

Causes of fetal anaemia

Mechanism of anaemia	Fetal examples
Failure of red cell production	Parvovirus B19 infection
	Alpha Thalassaemia major
	Fetal erythroleukaemia (eg trisomy 21)
	Congenital erythropoietic porphyria
Accelerated red cell destruction	Alloimmunisation (fetal haemolytic disease)
	Fetal G6PD deficiency
Loss of red blood cells (bleeding)	Fetomaternal haemorrhage
	TTTS and its variants
	Vasa praevia

Table 1

The breakthrough with screening for fetal anaemia came with the development of Doppler sonography. 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 the use of middle cerebral artery peak systolic velocity (MCA PSV) measurements into widespread mainstream practice for the non-invasive assessment of fetal anaemia. The middle cerebral artery is usually readily accessible for Doppler measurements, and the use of angle 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 taken. 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. As values exceed this threshold, the likelihood of significant fetal anaemia increases.

It must be recognised that the use of MCA PSVs is only a screening test for fetal anaemia, and there is a risk of both false positive and negative results. The overall accuracy of this test for predicting moderate and severe fetal anaemia has been quoted as 85%, which is 9% better than the use of serial amniocentesis and ΔOD450 estimations and also clearly avoids the risk and unpleasantness of multiple needle insertions. Furthermore, it is useful for detecting fetal anaemia from any cause, not just those causing haemolysis. However, the false positive rate is 12% and, although less common, false negatives do also occur. Nevertheless, it is now considered the gold standard for screening for fetal anaemia. Fetal blood sampling remains the diagnostic test.

In some circumstances, the fetal anaemia may only be recognised after birth. However, there is treatment available for prenatally diagnosed fetal anaemia distant from term. The first ever fetal intrauterine transfusions (IUTs) were performed into

Alec McEwan *MRCOG is a Consultant Obstetrician and Subspecialist in Fetal and Maternal Medicine at Nottingham University Hospitals NHS Trust, Nottingham, UK. Conflicts of interest: none declared.*

the fetal peritoneal cavity, from where, incredibly, the red cells were absorbed across the bowel wall to reach the fetal circulation. Alternatively, intracardiac transfusions were performed. With very significant improvements in real time ultrasound scanning, these routes are only utilised now in severe cases at extremely preterm gestations. More usually, at the time of fetal blood sampling from the umbilical vein, blood is transfused directly into the intravascular space, the volume determined by fetal size and haemoglobin. The quoted risk of complications (2%) increases to 5–20% in an hydropic fetus.

Case 1

A woman in her first pregnancy, with a previously straightforward antenatal course, presented at 38 weeks gestation with a three day history of reduced fetal movements. She had experienced no pain or vaginal bleeding, and her BP was normal and urine clear. Her uterus was soft and non tender on examination. A CTG was performed (Figure 1) and the registrar raised the possibility that the trace was sinusoidal and performed a vaginal examination with ARM. The patient was 3 cm dilated and the liquor was clear. Fifteen minutes later the decision was made to perform an emergency caesarean section. The baby was born 35 min later and was noted to be pale and floppy at delivery but required minimal resuscitation and was given Apgar scores of 8 at 1 min, 8 at 5 min and 9 at 10 min. The venous cord pH was 7.27 (BE -6.4) and the arterial pH 7.19 (BE -8.0). A review of the baby at 1 h of life was reassuring. However, 30 min later the baby was admitted to the neonatal unit pale and floppy and went onto develop seizures and required ventilation for 5 days. The haemoglobin on admission to the NNU was found to be 4.9 g/dl and a blood transfusion was given. A direct Coombs test was negative, however a maternal Kleihauer test was found to be strongly positive. A subsequent newborn MRI showed widespread ischaemic changes in the cortical deep and periventricular white matter, and the thalamocapsular region. These changes were indicative of an injury occurring a few days before birth. Limb stiffness was detectable by discharge and the parents were warned of a high chance of their child developing cerebral palsy. The obstetric and neonatal team concluded that the fetus had suffered a massive fetomaternal haemorrhage (FMH) at some point at least three days prior to delivery and that this probably occurred over a relatively short duration.

Fetomaternal haemorrhage (FMH)

FMH can be defined as the passage of fetal red blood cells across the trophoblast layer and into the maternal circulation, but also includes the movement of maternal erythrocytes in the opposite direction. Loss of fetal red cells into the maternal circulation occurs in most pregnancies but the volume of blood in the majority of cases is less than 0.025 ml. In less than 1% of pregnancies is the volume 15 ml or more. *Massive* FMH has been variably defined as a loss of >80 ml or >150 ml, and this occurs in approximately 1 in 1000 and 1 in 5000 births respectively.

There are two well established methods of measuring the size of a fetomaternal bleed. The Kleihauer–Betke screen relies on 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 the 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. This test is labour intensive and very imprecise, but nevertheless widely available. Flow cytometry is the second 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. This test is fast, and more accurate, but is not available universally, and often not out-of hours.

Sinusoidal CTG

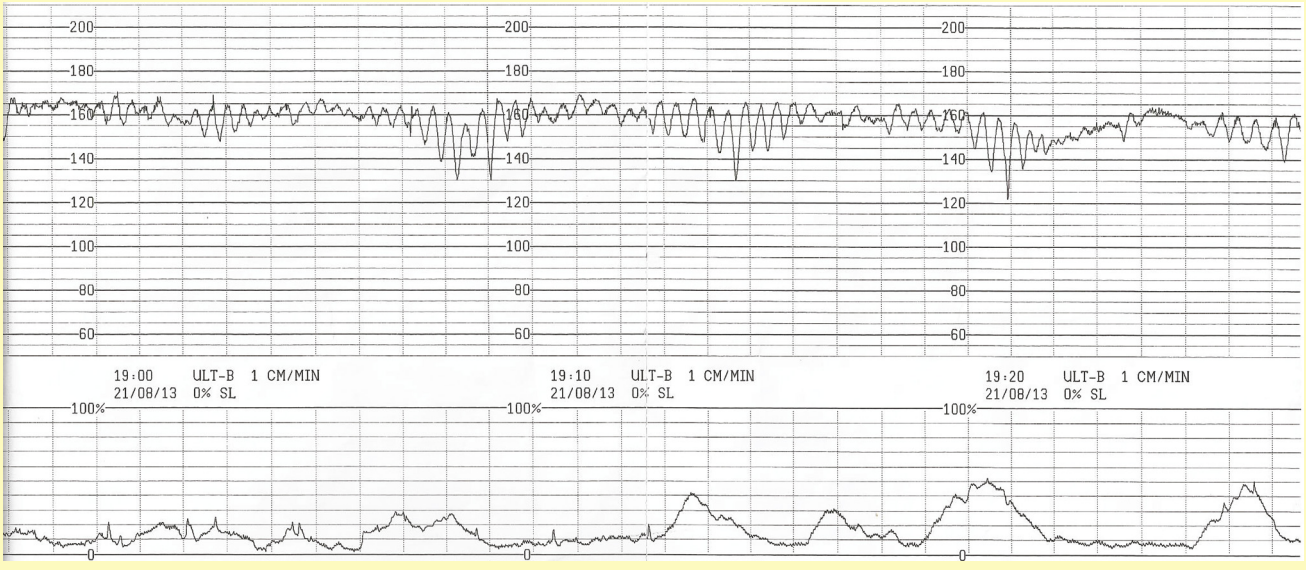

Figure 1