Management of foetal hydrops secondary to Kell isoimmunisation via foetal blood transfusion: a Doppler-guided approach

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ABSTRACT

We describe a male neonate with foetal hydrops due to foetal anaemia caused by Kell isoimmunisation. The severity of anaemia was monitored by Doppler ultrasonography of the middle cerebral artery peak systolic velocity, and this was used to time the foetal blood transfusions. The 33-year-old Indian mother received a total of five foetal blood transfusions from 21 weeks to 31 weeks of gestation, resulting in resolution of the anaemia and hydrops.

Keywords: foetal anaemia, foetal blood transfusion, foetal hydrops, Kell isoimmunisation, middle cerebral artery peak systolic velocity

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INTRODUCTION

Anti-Kell antibodies cause approximately 10% of cases of severe antibody-mediated anaemia in foetuses and newborns. The clinical manifestation of Kell isoimmunisation may start as early as 18 weeks of gestation and progresses quickly, resulting in severe foetal anaemia. The titre of anti-Kell antibody in maternal serum and the level of amniotic fluid bilirubin do not correlate well with the severity of foetal anaemia, unlike that in Rhesus (D) disease. We describe a case in which severe foetal hydrops due to anaemia from anti-Kell antibodies was managed with regular foetal blood transfusions, using Doppler studies of the peak systolic velocity of the foetal middle cerebral artery (MCA-PSV) to time and monitor each subsequent transfusion.

CASE REPORT

The patient was a 33-year-old Indian woman, gravida four, para one. She had an elective Caesarean section in 2003 for foetal macrosomia, and a suction evacuation of the uterus in 2005 for a pregnancy that was implanted over the Caesarean section scar. She had no other significant medical or surgical history of note. She had an early dating scan at seven weeks and five days of gestation, which established the estimated date of confinement for her pregnancy. Her screening blood tests were all normal – she was negative for thalassaemia, rubella, syphilis, hepatitis B and human immunodeficiency virus. She had no history of febrile illness or rash in her pregnancy. Combined first trimester screen indicated that she was at low risk for trisomies 21, 13 and 18.

The maternal blood group was A Rh (D+). In her antibody screen, there were anti-Kell antibody titres of 1:>1,024 and anti-c antibody titres of 1:4. Foetal hydrops was diagnosed at 20 weeks foetal anomaly ultrasonography (US) by the presence of gross foetal ascites and pericardial effusion, an enlarged left ventricle, a large liver and placenta, and polyhydramnios. She was subsequently referred to our tertiary centre. Further investigations included a Kleihauer test which indicated there was no foetal-maternal haemorrhage to account for foetal anaemia as a possible cause of hydrops. Her husband's blood group was O Rh (D+). Parvovirus IgG and IgM levels were normal, which excluded parvovirus-mediated suppression of marrow erythroblasts as the cause of foetal hydrops. Foetal karyotype was 46XY inv (9) (p11q13) which is a normal variant, thus the hydrops was not caused by a chromosomal disorder. Foetal heart rhythm was normal; this excluded arrhythmia as a cause for the hydrops.

The diagnosis was that of foetal anaemia from Kell isoimmunisation causing foetal hydrops. The pregnancy was monitored by regular twice-weekly Doppler US of the MCA-PSV and US assessment of ascites, amniotic fluid index (AFI) levels, pericardial and pleural effusions, and placental thickness (Table I). She received foetal blood transfusion if the MCA-PSV approached or exceeded 1.5 multiple of the median (MoM). In all, she received five foetal blood transfusions over a ten-week period from 21 weeks to 31 weeks of gestation (Figs. 1–3).

She was admitted to hospital at 33 weeks of gestation as the cardiotocograph (CTG) showed foetal heart rate abnormalities. Two doses of intramuscular dexamethasone of 12 mg each were administered to the mother to promote foetal lung maturity. The last US

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Table I. Resolution of US findings with serial foetal blood transfusions.

Date	Gestation	Ascites/cm	Pericardial effusion/mm	Pleural effusion/mm	Placental thickness/cm	Amniotic fluid index/cm
20.10.06	21 + 6	4.6	8.3	Nil	7	21
20.10.06	Transfusion #1					
2.11.06	23 + 5	1.7	7		5.4	
3.11.06	Transfusion #2					
6.11.06	24 + 2	2.3	6.8		4.9	21.8
20.11.06	26 + 2	1.48	3.8			
28.11.06	Transfusion #3					
30.11.06	27 + 5	3.1	3.7		5.7	
2.12.06	28	3.1	4		5.4	
4.12.06	Transfusion #4					
8.12.06	28 + 6	3.1	Not well seen		4.7	18.2
12.12.06	29 + 3	2.7	4.3		4.3	15.7
15.12.06	30.1	1.6	3.8			12.9
19.12.06	30.4	1.4	Nil		5.3	18.2
22.12.06	30.9	1.7	Nil			17.7
23.12.06	31.0	1.6	Nil			17.7
26.12.06	31.4	1.4	Nil			20
26.12.06	Transfusion #5					

just prior to delivery showed absence of foetal hydrops, pericardial effusion or ascites. The AFI was normal at 9.8 cm. A baby boy was delivered by urgent Caesarean section in view of the abnormal foetal heart rate trace at 33 + 2 weeks gestation. The newborn had a birth weight of 2,258 g. Apgar scores were nine at one minute and ten at five minutes. The baby was noted to be pink, well perfused and not oedematous. He cried at birth but had some subcostal retractions and was given facial oxygen. A grade 2/6 systolic murmur was present but lung fields were clear. The liver was enlarged to 4 cm and spleen 1 cm below subcostal margins.

The baby was placed on continual positive airway pressure ventilation for respiratory distress, and needed 30% oxygen. An initial arterial blood gas showed no acidosis. He was weaned to room air on day three of life. The baby had early jaundice for which it was placed on phototherapy for five days. Initial haemoglobin was 12.9 g/dL. Liver function tests were normal. No blood transfusion was required. Cranial US on day one was normal, with no intraventricular haemorrhage or parenchymal bleeds. A 2D echocardiogram performed on day one of life showed mild right ventricular hypertrophy. There was good biventricular contractility and no pericardial effusion. The baby was eventually discharged home well at two weeks of life.

The standard process of foetal blood transfusion is as follows: blood used for intrauterine transfusion underwent the same testing and preparation as for any transfusion. It was also irradiated to decrease chances of graft-versus-host reaction. The blood was screened to ensure it was cytomegalovirus-negative, and concentrated to a haematocrit of 75%–85% to reduce the total volume transfused to the foetus. In addition, it had to be type O Rh (D–) blood. Intravascular access was the most effective method of foetal transfusion. Access sites included the intrahepatic portion of the umbilical vein (used in our centre) or the umbilical vein at the placental end of the cord insertion. An alternative method would be foetal intraperitoneal transfusion, which was less effective.

The volume of blood for intravascular transfusion would depend upon the initial foetal haematocrit, the estimated weight of the foetus, the haematocrit of the transfused red blood cells and the target haematocrit. We aimed for a target haematocrit of 45%, as excessive blood viscosity in the foetus can lead to complications. The largest series of foetal transfusions reported from a single hospital comprised 740 intravascular transfusions in 254 patients. This series described a procedure-related perinatal loss rate of 1.6 percent and an overall rate of procedure-related complications (premature rupture of membranes, preterm delivery, infection, emergency caesarean delivery, perinatal death) of 3.1 percent per procedure.[1]

The mother was instructed to fast for at least six hours prior to the procedure, should an emergency Caesarean section be necessary for foetal heart rate abnormalities related to the procedure. One gram of intravenous cefazolin was given one hour before the procedure. Oral diazepam was administered for maternal sedation. The MCA-PSV was rechecked with US before the procedure. The mother was then placed in the left lateral position to prevent maternal hypotension. Foetal position was established with ultrasound. The mother's abdomen was

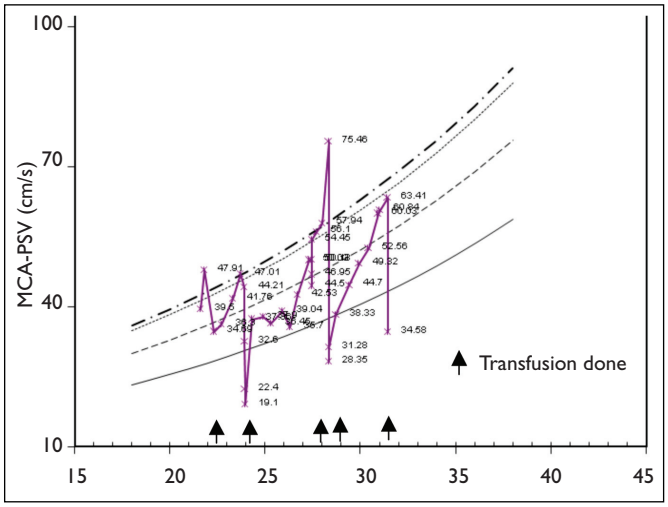

Fig. 1 Graph shows the trend of the middle cerebral artery peak systolic velocity (MCA-PSV) with transfusions.

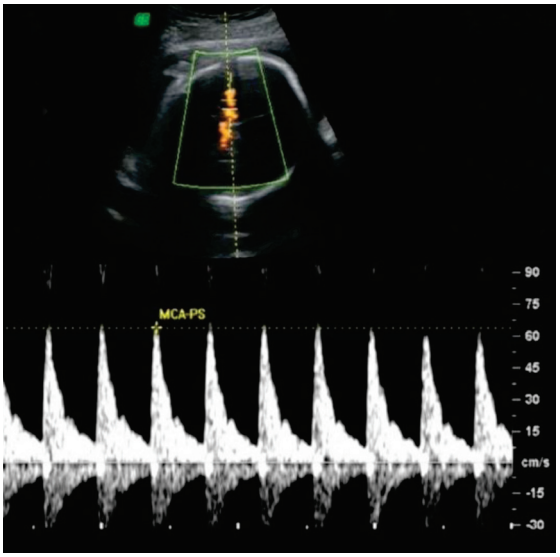

Fig. 2 Doppler US image done prior to the foetal blood transfusion shows a middle cerebral artery peak systolic velocity at 63.41 cm/s.

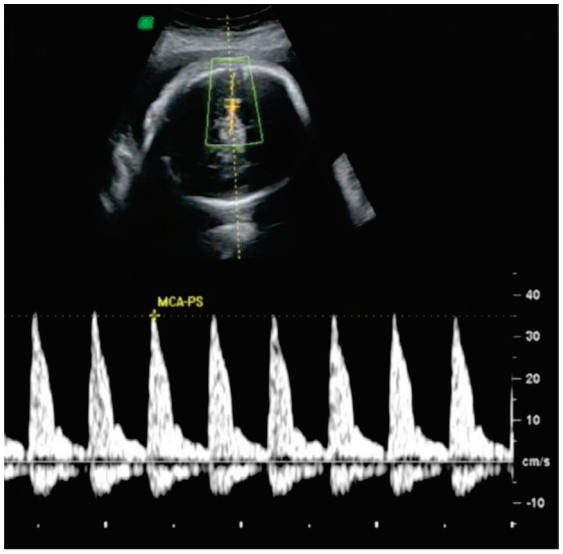

Fig. 3 Doppler US image done after the foetal blood transfusion shows a middle cerebral artery peak systolic velocity at 34.85 cm/s.

then prepped with iodine. Local anaesthetic was given to the skin as well as the mother's rectus sheath, under US guidance. The intrahepatic portion of the foetal umbilical vein was then identified, confirming with colour Doppler flow, and the vein was entered with a 20-gauge spinal needle. Foetal blood was aspirated to ensure correct placement in the vein. Intravenous pancuronium was then given for foetal paralysis; this improved the safety of the procedure and decreased the likelihood of foetal heart rate abnormalities. Foetal blood was taken to establish the initial foetal haematocrit with the i-STAT, a portable automated blood analyser (i-STAT, Abbott Laboratories, Abbott Park, IL, USA). An assistant prepared an infusion of packed red blood cells using a 10-ml syringe connected to a three-way stopcock, which connected the bag of blood and the extension tubing. A non-luer lock extension tubing was used to attach the three-way stopcock to the procedure needle. The foetal heart rate was monitored periodically to monitor for foetal bradycardia. After the transfusion was complete, a foetal blood sample was taken for post-procedure haematocrit on i-STAT as well as a formal full blood count. Intravenous frusemide was administered to the foetus, and foetal heart rate was checked again. A CTG was then performed to ensure that the foetal heart rate pattern was normal.

DISCUSSION

To date, foetal therapy has been successful in the treatment of foetal hydrops resulting from anaemia, twin-to-twin transfusion syndrome, cardiac arrthymias and hydrothoraces. Intrauterine foetal blood transfusion is the only therapy for hydrops resulting from foetal anaemia. Maternal Rhesus isoimmunisation and the development of anti-D antibody in the mother remain the classical example of maternal red blood cell isoimmunisation in subsequent pregnancies, resulting in erthyroblastosis foetalis and haemolytic disease of the newborn. Although the administration of antenatal Rh (D) immune globulin to the mother has significantly reduced the frequency of erythroblastosis foetalis and haemolytic disease of the newborn, Rh (D) still remains the most common cause of maternal red cell isoimmunisation.

Maternal red blood cell antibodies usually develop as a response to foreign red blood cell antigens via either previous blood transfusion to the mother or foetomaternal haemorrhage from a preceding pregnancy – in the form of either a miscarriage, stillbirth or live-birth. This is because many of these red blood cell antigens are already expressed on the foetal erythrocyte by the end of the

first trimester. Minor red blood cell antibodies are also associated with red blood cell antigens other than ABO and Rh (i.e. C, c, D, E, e). The Kell blood group is the most common of the minor red blood cell antibodies. The Kell antigen is present in 9% of Caucasian blood donors. Anti-Kell antibodies cause approximately 10% of cases of severe antibody-mediated anaemia in foetuses and newborns. The clinical manifestation of Kell isoimmunisation may start as early as 18 weeks of gestation and develops quickly, resulting in severe foetal anaemia.

Foetal anaemia in Rhesus disease occurs when maternal IgG antibody that is directed against an erythrocyte antigen crosses the placenta to cause destruction of foetal red blood cells. Anti-Kell antibodies do not cause foetal anaemia in this manner. In anti-Kell disease, foetal anaemia occurs by bone marrow suppression of the erythroid progenitor cells. As haemolysis is not the main mechanism of action as in Rhesus disease, bilirubin level in amniotic fluid are lower in anti-Kell disease. Thus, the titre of anti-Kell antibody in maternal serum and level of amniotic fluid bilirubin do not correlate well with the level of foetal anaemia, unlike in Rhesus disease.[2]

Spectrophotometry of amniotic fluid (ΔOD450) obtained by US-guided amniocentesis was the traditional (albeit indirect) method to assess for foetal anaemia in Rhesus haemolytic disease. The direct method of assessing foetal anaemia would be foetal blood sampling via cordocentesis (aspiration from the umbilical cord). Foetal blood sampling has been described as the only reliable tool to assess foetal anaemia in Kell isoimmunisation. In 2000, Mari et al described the use of Doppler US on the basis of an increase in the MCA-PSV as a useful non-invasive tool in the accurate detection of foetuses with moderate to severe anaemia. In their study, this measurement was found to predict the presence of moderate or severe anaemia in foetuses with a sensitivity of 100% and a false positive rate of 12%.[3]

The management of Kell isoimmunisation via the conventional approach of weekly US evaluation and measurement of maternal anti-Kell titres every 4–6 weeks has been compared with the Doppler assessment of the MCA-PSV which was performed 4–7 days. A MCA-PSV above 1.5 MoM was considered as an indication for foetal blood sampling.[4] Thus, MCA-PSV may be useful as a non-invasive tool to monitor pregnancies complicated by Kell isoimmunisation and to avoid invasive procedures like cordocentesis. It has also been demonstrated that in foetuses that have undergone one previous intrauterine transfusion, the timing of subsequent transfusions can be determined non-invasively by Doppler US on the basis of an increase in the MCA-PSV.[5]

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