

## **Case presentation slide seminar PPS 2008-01-24 Samantha Levine / Rosemary Scott University College Hospital London**

**A 30-year-old woman was Rhesus sensitised in her first pregnancy despite Anti-D being administered at delivery. During her second pregnancy with diamniotic dichorionic twins she was monitored for Rhesus antibodies ,given Anti-D at 17 weeks, 20 weeks, 22 weeks, 23 weeks, 24 weeks and 27 weeks and followed with serial ultrasounds. At 30/40 the MCA velocities in both twins significantly worsened indicating anaemia and 3 intrauterine blood transfusions were performed. At 34/40 there was intrauterine death of twin 1 and both were delivered by caesarean section. The surviving twin requiring neonatal intensive care for haemolytic disease of the newborn, respiratory distress syndrome, hypoglycaemia, ascites and inspissated bile syndrome..**

### **Diagnosis: Rhesus Alloimmunisation**

#### **Discussion**

**In 1941 Levine, Katzin and Burham demonstrated that antibodies to the Rhesus D antigen in the pregnant woman caused haemolysis and anaemia in their offspring. Due to the finding of a large number of immature nucleated red blood cells within the neonatal circulation, this was called Erythroblastosis Fetalis, now known as Haemolytic Disease of the Newborn. The high morbidity and mortality in this disease is not only because of the severe anaemia secondary to haemolysis but also due to hyperbilirubinaemia causing kernicterus.**

**The formation of maternal antibodies, called alloimmunisation, occurs when a Rhesus negative mother develops an immunological response to paternally derived Rh D antigen foreign to the mother and inherited by the fetus. The Rh D antigen is considered the most immunogenic of the antigens found on the surface of the human red blood cell. The maternal IgG antibodies formed thus, cross the placenta, bind to the antigens on the fetal red blood cells and can cause haemolysis.**

**The Rh D – negative blood group is found in approximately 15% of Caucasians, 3-5% of black Africans and is rare in Asians. One of the great success stories of modern perinatal care was the introduction of prophylactic post-partum Rhesus immune globulin (Anti-D immunoglobulin). About 17% of RhD-negative woman who do not receive prophylaxis become immunised. Over 90% of immunisation occurs from fetomaternal haemorrhage at delivery and the majority of the remaining 10% occurs in the third trimester. < 0.1 ml of fetomaternal haemorrhage is sufficient to cause immunisation. Currently in the U.K the incidence of rhesus haemolytic disease is 1/1000 births (0.1%).**

**The ABO, the Rh D status and antibody screen should be determined at the initial prenatal/antenatal visit. If the woman is Rhesus negative and the antibody screen negative Rh D immune globulin should be administered**

antenatally and post- partum depending on local clinical practise and the Rhesus status of the infant established from cord blood.

Anti-D immunoglobulin prophylaxis prevents alloimmunisation in > 99% of cases. Despite this a review of the 2002 birth certificates in the United States by the Centers for Disease Control indicated an incidence of Rh sensitisation of 6.7/ 1000 live births. Most failures are due to omission, insufficient dosing and lack of use for other antenatal indications for RhIG.

Despite the routine use of antenatal and postnatal RhIG prophylaxis its mechanism of action is still unclear. In 1960 investigators in both the U.K and USA independently thought that it might be possible to prevent Rh D immunisation with passive Anti-D. However, their rationales were different. In the U.K IgG anti-D was given to clear D+ red blood cells from the circulation. In the USA the approach was based on antibody-mediated immune suppression (AMIS). Advances in immunology suggest that prophylactic Anti-d works by both rapid macrophage-activated clearance of Anti-D coated red blood cells and/or by down regulation of immature dendritic cells or anti-D- specific B cells before development of the Anti-D response occurs.

If RhD antibodies are detected in the maternal circulation, she is considered alloimmunised. Mild- to-moderate haemolytic anaemia and hyperbilirubinaemia occur in 25-30% of fetuses/neonates in this scenario and 25% of these will develop hydrops. With correct management, the perinatal survival in cases of anaemia is >90% and if hydrops is present survival is often >80%.

In the past treatment strategies included premature delivery followed by exchange transfusion of the infant. In later years infusion of red blood cells directly in to the fetal peritoneal cavity was performed with their absorption via diaphragmatic lymphatics. Since the 1980s direct intravascular transfusion of red blood cells into the fetal umbilical cord under ultrasonographic guidance has improved perinatal survival to 85-95%

Improvement in treatment resulted in the need for diagnostic techniques to detect fetal anaemia requiring intervention. Initially amniocentesis was used to measure levels of amniotic-fluid bilirubin as an indirect measure of the destruction of fetal red blood cells. The advent of ultrasonographic directed access to the fetal umbilical cord (cordocentesis) allowed direct assessment of the fetal haematocrit. The search for a non-invasive method led to the current screening method of choice. In fetal anaemia decrease blood viscosity leads to increased venous return with increased blood flow velocity in all vessels. Degree of anaemia correlates with blood velocity. The vessel used to measure velocity is the middle cerebral artery (MCA) which is easily visualised by ultrasound. A peak velocity in the MCA expressed as more than 1.5 multiples of the median (MoM) has a sensitivity of 100% and a specificity of 86% for detecting moderate or severe anaemia.

Other workup investigations include determining the genotype of the father of the fetus and fetal Rh D determination from amniocytes or analysis of fetal DNA found in maternal blood. Maternal Rh D antibody titres also correlate somewhat with the risk of anaemia/hydrops.

Once fetal anaemia is suggested by the above investigations intrauterine transfusion may be performed together with planning the optimum timing for delivery. The risk of fetal death is 1-2% per transfusion procedure. The haematocrit decreases about 1% per day post transfusion in the anaemic

**alloimmunised fetus and following 3 transfusions 99% of the fetal blood is replaced by adult transfused blood.**

## **Summary**

**Haemolytic disease in the newborn is a rare disease in the U.K due the introduction of screening for maternal Rhesus D status and the development of Rhesus immune globulin (anti-D) to prevent maternal alloimmunisation. In this case the persistence of maternal rhesus antibodies was probably due to an inadequate dosage of ant-D being administered after delivery of her first child. Despite close monitoring during this pregnancy and intrauterine blood transfusions, one of the twins died and the post mortem demonstrated the consequences of the severe anaemia suffered. The infant was hydropic with a dilated right heart. There was massive extramedullary haematopoiesis enlarging the liver and spleen and hypoxic ischaemic brain injury. Blood in the peritoneal cavity resulted from the therapeutic use of intraperitoneal blood transfusions. The surviving twin had severe haemolytic disease of the newborn but the development of kernicterus appears to have been avoided by aggressive therapy for hyperbilirubinaemia. Whether there is long term neurological sequelae in this twin remains to be determined.**