Haemolytic Disease of the Fetus and Newborn

Synonyms: rhesus haemolytic disease, erythroblastosis fetalis, haemolytic disease of the newborn (HDN)

Haemolytic disease of the fetus and newborn (HDFN) is a condition which results from transplacental passage of maternal antibodies which cause immune haemolysis of fetal/neonatal red blood cells.

Pathogenesis

The antibodies responsible for haemolysis can be naturally occurring (eg, anti-A or anti-B antibodies) or can develop as a result of a sensitising event such as pregnancy or transfusion. The most well recognised is rhesus alloimmunisation (Greek: allo = ‘other’ or ‘different from’) which begins with red blood cells from a rhesus-positive fetus crossing the placental barrier during pregnancy and delivery, and entering the maternal blood circulation. A rhesus-positive father and a rhesus-negative mother are required for this situation to develop. The incompatible antigens introduced result in a primary immune response and stimulate the production of maternal antibodies. A very small amount of fetal-maternal haemorrhage (FMH) needs to occur (less than 0.1 ml) and most go unrecognised. Primary exposure can also be the result of amniocentesis, chorionic villus sampling and cordocentesis.

Several fetal rhesus antigens may cause alloimmunisation (c, C, d, D, e and E) and this can also occur with the Kell, Duffy, ABO and other blood group systems. The vast majority of haemolytic disease used to be caused by the rhesus D antigen but the incidence has reduced significantly with the administration of Rh immunoglobulin to rhesus-negative women during pregnancy and shortly after birth of a rhesus-positive baby.[1] Consequently, ABO incompatibility is now the single largest cause of HDFN in the western world.[2]

There are rarely any problems during primary exposure but subsequent pregnancies result in large amounts of maternal anti-D antibodies being produced and the risk increases with each gestation. These are capable of crossing the placenta, where they affix to fetal red blood cells, which then become recognised as 'foreign' by the fetal immune system and haemolysed by fetal macrophages and lymphocytes. If the rate of red cell destruction exceeds the rate of production it results in fetal anaemia which, if severe, can lead to fetal heart failure, fluid retention and swelling (hydrops). Red cell breakdown results in bilirubin release which is not a problem during fetal life as it is cleared by the placenta. After birth, however, the immature neonatal liver is not capable of handling a high bilirubin load and this can result in severe neonatal jaundice. High levels of jaundice if untreated can result in permanent brain damage (kernicterus) because of deposition of bilirubin in certain areas of the neonatal brain.

Epidemiology

The incidence of haemolytic disease of the newborn (HDN) depends on the proportion of the population who are RhD negative. This varies within ethnic minorities but, in the UK, it is highest in the Caucasian population (approximately 16%).

Before immunoprophylaxis was available, HDN affected 1% of all newborns and was responsible for the death of one baby in every 2,200 births.[3]

Anti-D prophylaxis (mostly administered postnatally) and advances in neonatal care have reduced the frequency of HDN by almost a factor of 10 to 1 in 21,000 births.[4] Deaths attributed to RhD alloimmunisation fell from 46/100,000 births before 1969, to 1.6/100,000 in 1990.[5] This may not be entirely attributable to immunoglobulin; changes in abortion rates and racial composition may also play a part.

One American study quoted a prevalence of RhD alloimmunisation of 6 in 1,000 births and suggests that this should now be considered a rare condition.[6]

Risk factors[4, 5]

- Alloimmunisation during first pregnancy.
- Alloimmunisation during second or subsequent pregnancy.
- Failed prophylaxis.
- Over 99% of women have an FMH of less than 4 ml at delivery. 50% of women (who have larger FMHs) have them after normal deliveries. However, the following clinical circumstances are more likely to be associated with large FMH:
  - Traumatic deliveries including caesarean section.
  - Stillbirths and intrauterine deaths.
  - Abdominal trauma during the third trimester.
  - Multiple pregnancies (at delivery).
  - Unexplained hydrops fetalis.

Presentation[4]
Antenatally, the first indication of the condition is the presence of anti-D antibodies in the mother as detected by the indirect Coombs’ test. All rhesus-negative women have this test performed in the UK at the first antenatal visit.

Routine ultrasound screening may detect hydrops fetalis (see below) or polyhydramnios.

Infants born to alloimmunised mothers may appear clinically normal in mild cases. Diagnostic findings include jaundice (yellow amniotic fluid, yellow vermix, yellow skin), pallor and hepatosplenomegaly. Kernicterus (bilirubin encephalopathy) is a serious risk and hypoglycaemia is common. Hydrops fetalis may present antenatally as polyhydramnios (excessive amniotic fluid) or postnatally with subcutaneous oedema, pericardial effusion, pleural effusion, ascites and hepatosplenomegaly. The placenta may be thickened.

Infants born after intrauterine transfusion for prenatally diagnosed HDFN may be severely affected and may have very high levels of cord bilirubin. Clinical signs of severe haemolytic disease are pallor, hepatosplenomegaly, oedema, petechiae and ascites.

**Differential diagnosis[7]**

**Other causes of HDN**
- Rh system antibodies.
- ABO system antibodies.
- Kell system antibodies.
- Duffy system antibodies (rare).
- MNS and s system antibodies (rare).

**Other causes of neonatal jaundice**
- Intrauterine congenital infections (syphilis, cytomegalovirus, parvovirus).
- Erythrocyte membrane defects.
- Red blood cell enzyme deficiencies.
- Enclosed haemorrhages.
- Hypothyroidism.
- Gastrointestinal obstruction.
- Metabolic diseases.

**Causes of non-immune hydrops fetalis**
- Anaemia.
- Cardiac failure from dysrhythmia.
- Congenital heart defects.
Investigations

- **Indirect Coombs' test** should be performed at the first antenatal visit, for all rhesus-negative mothers. If the test is positive, antibody titres should be monitored with serial samples.
- Another option is non-invasive rhesus genotyping of the fetus using free cell fetal DNA obtained from maternal blood, which identifies pregnancies at risk of sensitisation. This can be reliably done and is available in the UK but is not currently universal practice. [8, 9]
- **Antenatal ultrasound** may detect signs of hydrops fetalis (see above). Doppler ultrasound of the middle cerebral artery has largely replaced fetal blood sampling as an initial test for the detection of fetal anaemia. [10]
- **Fetal blood sampling**: if the Doppler scan confirms anaemia, fetal blood sampling should be considered. The sample can be taken at the site of cord insertion or from the hepatic vein. The procedure is done under the guidance of ultrasound imaging. The intrahepatic site causes less fetal distress but is technically more difficult. Fetal loss varies from 1-20% depending on the site of sampling and the condition of the fetus.
- **FBC** shows:
  - Anaemia, increased nucleated red blood cells and other red blood cell abnormalities, which may be seen.
  - The reticulocyte count can be as high as 40% in severe cases.
  - If there is extensive disseminated intravascular coagulation, schistocytes and burr cells may be observed and neutropenia and thrombocytopenia may occur.
- **Biochemical indices should be analysed**: hypoglycaemia may be the result of islet cell hyperplasia and hyperinsulinism secondary to the release of metabolic byproducts from lysed red blood cells.
- **Postnatal diagnosis**: immediately after birth of any baby to a rhesus-negative woman, blood from the umbilical cord or from the baby should be checked for ABO and Rh blood group, direct Coombs' test, haemoglobin and baseline bilirubin. A positive Coombs' test in the presence of ABO or Rh incompatibility supports the diagnosis.

Management

**In utero**

As soon as the blood samples confirm anaemia, transfusion should be commenced with group O negative packed cells cross-matched with maternal blood. This is best done at 18 weeks but samples can be taken at 16 weeks if necessary. Intravenous transfusion under ultrasound guidance via the umbilical vein is to be preferred to the intraperitoneal route, as the latter is more difficult in an hydropic fetus and causes more complications. Further transfusions should be dictated by serial Doppler scans. Following successful transfusion, delivery should be anticipated between 37-38 weeks. If complications arise, delivery at 32 weeks should be considered. The mode of delivery can be dictated by obstetric considerations. [3]

Future therapy will involve selective modulation of the maternal immune system, making the need for intrauterine transfusions a rarity. [6]

**After delivery** [3]

- 50% of babies born to mothers with high maternal antibody titres have normal haemoglobin and bilirubin levels but should be monitored for the onset of late anaemia at 6-8 weeks.
- 25% have moderate disease and may require transfusion. Significant hyperbilirubinaemia may develop within the first 24 hours after birth, which may require phototherapy to avoid kernicterus.
- The remaining 25% will have severe disease and either be stillborn or have hydrops fetalis.
- When severe HDFN is anticipated, the birth should be attended by a paediatrician trained in neonatal resuscitation and fresh O negative blood should be immediately available. The baby with severe haemolytic disease requires immediate resuscitation and supportive treatment including temperature stabilisation followed by exchange transfusion. Further top-up blood transfusions and phototherapy may be needed.
- Early administration of intravenous immunoglobulin (IVIg) in babies with severe haemolytic disease has been shown to reduce haemolysis, peak bilirubin levels and the need for exchange transfusion. [11]

Complications

The late sequelae of kernicterus (extrapyramidal, auditory and visual abnormalities and cognitive deficit) occasionally occur but are rarely seen with the success of modern treatment. [5] Other potential complications include late-onset anaemia, graft-versus-host-disease, infections and various metabolic abnormalities.

Portal vein thrombosis and portal hypertension may occur in children undergoing exchange transfusion. [12]

One meta-analysis showed a significant link between feto-maternal rhesus incompatibility and schizophrenia. [13]

Prognosis

Overall survival has been noted to be 84-90%. [3] Reversal of hydrops as a result of intrauterine treatment is associated with improved perinatal outcome but, when it does not reverse, the survival rate is only 39%. [3]

Neurodevelopment is usually normal (for >90%). [14]

Prevention [4, 5]
Routine antenatal anti-D prophylaxis (RAADP) using anti-D immunoglobulin should be given to all rhesus-negative women who have not already been sensitised. It can be given as two doses of anti-D immunoglobulin of at least 500 IU at 28 and 34 weeks or as a large single dose of 1500 IU at 28 weeks gestation. Treatment is also indicated after other sensitising events such as abortion, miscarriage, amniocentesis, ectopic pregnancy, and abdominal trauma.

Following birth ABO and Rh D typing should be done on cord blood and if baby is confirmed to be D positive, all D negative, previously non-sensitised women should be offered at least 500 IU of anti-D immunoglobulin within 72 hours of delivery. Maternal blood samples should be checked for FMH and additional dose given guided by FMH results.

See separate Anti-D (Rho) Immunoglobulin article.

Further research into anti-D that is not from human plasma is required. [14]

History

HDN was first described by a French midwife, in a set of twins in 1609. It was later termed erythroblastosis fetalis when Louis K Diamond and his co-workers recognised the relationship between erythroblasts in the circulation, anaemia, fetal hydrops and jaundice. The rhesus blood group system was identified in 1940 and the link between rhesus haemolytic disease and alloimmunisation was recognised in 1953.

Further reading & references

- High-throughput non-invasive prenatal testing for fetal RHD genotype; NICE Diagnostic Guidance (November 2016)
- Routine antenatal anti-D prophylaxis for women who are rhesus D negative; NICE Technology Appraisal Guidance, August 2008.
- BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn, British Committee for Standards in Haematology (Jan 2014)

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