Haemolytic Disease of the Newborn

Information for Healthcare Professionals

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All views expressed are the author’s own.

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**Introduction**

**A typical scenario:**

“I am 31 years old and 37 weeks pregnant with my first child. I have just found out that I have antibodies in my blood. My friend lost her second child to this. Now my infant is at risk. We are devastated. Are there more people like us?”

**Definition**

Haemolytic disease (HD) is a condition peculiar to pregnancy, where the maternal immune system produces IgG antibodies in response to the accidental presence of fetal red cell antigens in her blood. If undetected in pregnancy, the condition can prove harmful to the unborn fetus with significant morbidity, permanent neurological damage and/or mortality. However, if detected in sufficient time, treatment is available which can prevent these problems.

The focus of this information is about the role of the healthcare professional in managing the care of the woman who has developed antibodies during her pregnancy. The term healthcare professional in most instances will be the woman’s midwife and clinician or fetal medicine specialist (obstetrician) for specialised in-utero management.

**Prevalence**

Data gathered by Dutch researchers within the past 6 years shows that 1.2% of pregnancies are affected by the presence of red cell antibodies. Antibodies of less clinical significance are present in up to 4% of women.

**Blood groups, antigens and antibodies**

**Blood groups**

The ABO and Rhesus (Rh) system comprise 33 major blood types, groups/systems of which the Rh system is the most important.

A blood group, defined by the International Society of Blood Transfusion ISBT is one that is:

“controlled at a single gene locus or by two or more very closely linked homologous genes with little or no observable recombination between them.”

The Rhesus (Rh) antigens - The Rh group or system is comprised of several antigens namely ‘C’, ‘c’, ‘D’, ‘E’ and ‘e’ (there is no ‘d’ antigen, merely the absence of the D protein on the red cells) which can cause mild to severe disease. The gene for Rh is situated on the upper portion of chromosome 1 (location p36.11).

If the antigen is present (antigen positive), the individual is Rh D positive (RhD +ve). Conversely, without antigen, they are Rh D negative (RhD -ve). In Europe around 85% of people are RhD-positive and 15% RhD-negative.

**Antibodies** - Over 60 different types of red cell antibodies exist to date which the maternal immune system can produce if a small amount of fetal blood enters the maternal circulation. Anti-D is the commonest.

Some pregnancies can be affected by the presence of more than one antibody. Whilst anti-bodies in isolation are concerning, multiple antibodies are likely to cause more severe HD.

Antibodies to non-Rh antigens include Kell (K), Duffy (Fya) and anti-Jka (Kidd), named after the individuals who discovered them. Anti-K antibodies can cause fatal anaemia even at low levels/titre by suppression of erythropoietin production. All remaining antibodies in this category tend to be less severe.

**Fetal red blood cells** - The fetus produces megaloblastic red blood cells (RBC) early in development, which become normoblastic near term. The life span of a fetal RBC is approximately 80 days. Expression of the Rh antigen starts about 40 days of gestation.
**Rhesus allo-immunisation (sensitisation)**

**First pregnancy**

**Sensitisation** - If a woman is RhD negative and the fetus RhD positive, then just a small amount of fetal blood escaping into her circulation across the placenta can cause ‘isoimmunisation’ otherwise known as ‘sensitisation’. Seepage and mixing of as little as 0.1 ml of fetal blood (treated as ‘foreign’ by the maternal immune system), can stimulate the formation of maternal Anti-D IgG antibodies. These act in the same way as do other antibodies in response to many other conditions that may threaten our health e.g. the common cold. The aim of these pregnancy antibodies therefore, is to fight and destroy all ‘invading’ Rhesus positive antigens in the maternal blood. Unfortunately these antibodies can also cross the placenta and destroy RhD positive fetal RBCs causing fetal anaemia.

To prevent this from happening, anti-D immunoglobulin can be given as soon as possible, or within 72 hours, after a sensitising event such as vaginal bleeding, to destroy the fetal RhD antigens.

This exogenously administered Anti-D can prevent the sensitisation process from happening by removing the fetal red blood cells before the woman’s immune system responds.

**Hydrops fetalis** - The severity of HD depends on the type of antibody, the paternal genotype, the gestation and condition of the fetus at diagnosis. Depending on the type, level/titre of antibodies present and the rate of haemolysis and ability of the fetus to make new RBC the fetus may become mildly, moderately or severely anaemic and/or jaundiced.

‘Hydrops fetalis’ develops as a consequence of severe fetal anaemia and is due to accumulation of excess fluid in two or more body areas of the fetus such as scalp oedema, pleural and pericardial effusion and abdominal ascites. Babies delivered to women with antibodies to fetal antigens may develop jaundice, severe anaemia, and kernicterus.

**Antenatal management**

**The midwifery ‘booking’ visit consultation**

**History taking and screening tests** - As part of the antenatal package of care, the ‘booking visit’ is a key consultation for gathering specific information about the woman’s health: during her current and past pregnancies; familial history and her recreational habits. Baseline observations and blood are also taken with her consent to screen for known medical, chromosomal or genetic conditions including a pinked topped EDTA sample to:

- Determine the woman’s Blood group/type and Rh type
- Identify the presence of antibodies
- Quantify antibody levels/titres if present
- Minimise any cross-matching issues should blood for transfusion be needed

**Antibody card** - All Rhesus negative women are issued with a special card that includes information about their blood group, Rhesus and antibody type on the front.

**Paternal and fetal genotyping** - Either paternal or fetal genotyping can be undertaken to determine the Rhesus status of the fetus. However, the woman and her partner should be carefully counselled beforehand.

If Rh positive, the genetic father can either be ‘heterozygous’ - autosomal recessive (Dd) or ‘homozygous’ - autosomal dominant (DD). If the latter, then there is a 100% chance of the fetus and any other younger offspring (assuming the woman becomes pregnant by the same man) being affected. Anti-D immunoglobulin is recommended in this case.

If there are any doubts regarding paternity, or the genetic father of the fetus cannot provide a blood sample, a test using cell free fetal DNA (cffDNA) can be used to identify the fetal D status with great accuracy. This has been developed using a maternal peripheral blood sample usually taken at the 15-17 week prenatal visit, it is reliable from 11 weeks gestation and can be offered to women of up to 26 weeks gestation. Occasionally, the test fails in which case a repeat test or amniocentesis can be offered. If either are declined, the pregnancy should be considered at ‘high risk’ and managed accordingly.

Amniocentesis and chorionic villus sampling (CVS) are offered with caution as needling can induce a miscarriage.
Screening: Consent process

The healthcare professional should always aim to give an unhurried and clear explanation about the nature, purpose, risks and benefits, timing, limitations and potential consequences of all antenatal screening tests. Additionally, the woman should be offered unbiased, up to date, high quality test-specific written information. Ideally, information should be available in different formats i.e. illustration, alternate languages, DVD, CD, braille. For the process to be viable, consent is only valid when the woman has had enough time to consider all the information given to her and make a decision that she feels is right for her.6

When to refer to a clinician or fetal medicine specialist

Referral to a fetal medicine specialist with knowledge and expertise of Rhesus disease should be made by the healthcare professional during the consultation if the woman has had:

- a previous antibody affected pregnancy;
- a previous anaemic fetus;
- a fetus that required in-utero transfusion (IUT);
- an unexplained severely jaundiced infant;
- an infant that required a blood or exchange transfusion
- an intrauterine or neonatal death from Rhesus disease.

The gestation at which any IUTs were undertaken or age at which phototherapy, blood or exchange transfusions is also important to know in order for the clinician to develop a plan of care. It is also relevant to note the possible reasons why antibodies developed. Maybe the woman was not offered anti-D prophylaxis or perhaps not enough was given or maybe it was because of other reasons as listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1: When sensitisation can occur and anti-D immunoglobulin is given to a Rhesus negative woman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Following a miscarriage</td>
</tr>
<tr>
<td>After termination of pregnancy</td>
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<tr>
<td>Following an antepartum haemorrhage</td>
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<tr>
<td>Following an accident e.g. fall, car-crash</td>
</tr>
<tr>
<td>After any type of prenatal invasive testing or therapy</td>
</tr>
<tr>
<td>Following a ‘normal’ vaginal, instrumental or surgical delivery</td>
</tr>
<tr>
<td>External cephalic version for breech presentation</td>
</tr>
</tbody>
</table>
Results

**Blood: Rising antibody levels/titres and sonographic examination**

Prompt action and referral to a fetal medicine specialist are required if the woman’s antibody level/titre rises beyond the specified laboratory cut off level as it is known that increasing levels/titres correlate with fetal anaemia (Table 2).

### Table 2: Antibody type and action to take for specific maternal serum levels

<table>
<thead>
<tr>
<th>Antibody type</th>
<th>Levels/Titre iu/ml</th>
<th>Severity</th>
<th>Referral to Fetal Medicine Specialist</th>
<th>Timing of serial samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>&lt; 7.5</td>
<td>Mild</td>
<td>Not immediately needed</td>
<td>Every 4 weeks up to 28 weeks, then every 2 weeks until delivery</td>
</tr>
<tr>
<td></td>
<td>&gt; 7.5 - &lt; 20</td>
<td>Moderate risk</td>
<td>Yes</td>
<td>Every 4 weeks up to 28 weeks, then every 2 weeks until delivery</td>
</tr>
<tr>
<td></td>
<td>&gt; 20</td>
<td>Severe risk</td>
<td>Yes</td>
<td>Every 4 weeks up to 28 weeks, then every 2 weeks until delivery</td>
</tr>
<tr>
<td>D</td>
<td>&lt; 4</td>
<td>Mild - unlikely to develop HDN</td>
<td>Not immediately needed</td>
<td>Every 4 weeks up to 28 weeks, then every 2 weeks until delivery</td>
</tr>
<tr>
<td></td>
<td>&gt; 4</td>
<td>Yes</td>
<td></td>
<td>Every 4 weeks up to 28 weeks, then every 2 weeks until delivery</td>
</tr>
<tr>
<td></td>
<td>&lt; 15</td>
<td>Moderate</td>
<td>Yes</td>
<td>Every 4 weeks up to 28 weeks, then every 2 weeks until delivery</td>
</tr>
<tr>
<td></td>
<td>&gt; 15</td>
<td>Moderate</td>
<td>Yes</td>
<td>Every 4 weeks up to 28 weeks, then every 2 weeks until delivery</td>
</tr>
<tr>
<td>E</td>
<td>See note in ‘referral’</td>
<td>Mild</td>
<td>No - only if anti c present</td>
<td>Retest at 28 weeks</td>
</tr>
</tbody>
</table>

**Ultrasound: Hydrops**

Similarly, if the fetus shows sonographic signs of (see image 1 and 2): excess fluid within the abdomen (ascites), fluid around the lungs or heart (pleural and pericardial effusions); cardiomegaly (enlarged heart), polyhydramnios or fluid beneath the skin surrounding the scalp and/or body (oedema) on ultrasound, it is possible the fetus is anaemic. Again, prompt referral to a fetal medicine specialist is necessary to minimise further suppression of erythropoiesis.

Image 1: Longitudinal view of fetus  
Image 2: Cross-sectional view of fetus at the thoracic level of the spine

A = fluid beneath the skin - scalp and body  
B = face  
C = fetal heart  
A = pleural effusions  
B = lungs  
C = fetal spine

Treatment and management of HD

Fetal surveillance for ‘moderate’ or ‘severe’ HD should be undertaken (usually 1-2 weeks and antibody quantification) to predict the risk of fetal anaemia. Often units will monitor the fetus and then refer to a fetal medicine unit for transfusion once the MCA Dopplers are fast indicating anaemia. The fetal medicine unit must have the appropriate invasive skill set to undertake intrauterine transfusion if necessary.

Middle Cerebral Artery Peak Systolic Velocity (MCA PSV) Doppler - A non-invasive technique for measuring fetal blood flow velocity, the Middle Cerebral Artery Peak Systolic Velocity (MCA PSV) Doppler is used from 23 to 35 weeks to assess fetal wellbeing. Rising or maximum MCA PSV velocities against ‘Mari’s Curve’ indicate when a fetus is becoming anaemic before hydrops develops allowing timely in-utero transfusion.8

Preparation for intrauterine transfusion - At least 24 hours (1 day’s ‘working notice’) should be given to the transfusion laboratory for a planned IUT. If the woman has rare antibodies, then the transfusion laboratory needs to know in order to source suitable blood from another laboratory. Adult serum-free O negative packed red donor cells, cross matched against the mother’s blood type is prepared for the transfusion. However, for non-planned cases, emergency blood can be prepared. The woman needs to be carefully counselled as to the risks and benefits of the procedure including the possible need for emergency delivery should complications develop during transfusion after 24 weeks’ gestation.

Intrauterine transfusion (IUT) procedure - By extracting a small amount of fetal blood from the umbilical cord of fetal intrahepatic vein (known as cordocentesis or percutaneous umbilical blood sampling [PUBS]) using a 6 inch long, 23 gauge ‘echo-tip’ needle (see image 3) the fetal haemoglobin concentration (Hb) can be measured to determine whether the fetus is mildly (>7 g/dl), moderately (2-7 g/dl) or severely (<2 g/dl) affected. The needle is inserted through the maternal abdomen into the umbilical vein at the placental cord insertion, intra-hepatic vein, direct into the fetal heart of loop of cord (see image 4). The procedure is carried out under direct ultrasound guidance to minimise complications listed in Table 3. Blood is then steadily infused into the fetus until the fetal haemoglobin level is restored to normal levels. Fetal transfusion carries approximately a 2% risk of fetal loss which rises considerably if the fetus is hydropic.9

Table 3: Overall pregnancy risks of cordocentesis and intrauterine transfusion

<table>
<thead>
<tr>
<th>Risk Event</th>
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<tbody>
<tr>
<td>Fetal bradycardia</td>
</tr>
<tr>
<td>Limb abnormalities</td>
</tr>
<tr>
<td>Respiratory difficulties post delivery</td>
</tr>
<tr>
<td>Miscarriage, intrauterine death</td>
</tr>
<tr>
<td>Premature delivery</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Haematoma - cord, placenta</td>
</tr>
<tr>
<td>Haemorrhage - cord, placenta, fetus</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Premature rupture of membranes (PROM)</td>
</tr>
<tr>
<td>Further rise in antibodies</td>
</tr>
<tr>
<td>Maternal death</td>
</tr>
</tbody>
</table>

Timing mode and place of delivery

Naturally, the woman will feel anxious about the birth and after care of her infant and so plentiful support and information should be available to help alleviate and answer any of her concerns. A visit to the neonatal unit should also be arranged.

The mode of delivery is at the obstetrician’s discretion to ensure that the fetus is delivered in optimum condition. Decisions will also include the expert views and opinions of the neonatal team, who after delivery will manage the anaemic infant.

Clinicians generally prefer to deliver after 34 weeks gestation when the fetal lungs have matured. Table 4 shows the general plan of care for the timing and place of delivery for an antibody affected pregnancy.

At birth, a cord blood sample should be taken for Hb, ABO and Rhesus typing, bilirubin and the Direct Anti-globulin Test (DAT) also called the Coombs’ test. If the latter is positive, the infant’s bilirubin should also be measured as its red cells will be coated with antibodies. Results will then determine whether phototherapy or exchange transfusion is required.
Neonatal management - Haemolysis can continue for some time after birth due to the woman's passively acquired antibodies present in the infant's blood. Anaemia can also present later after birth, despite IUT therapy during pregnancy.

Phototherapy is the first-line treatment for jaundice but if bilirubin levels continue to rise, exchange transfusion will be required. Some infants, especially those who have had multiple transfusions, may not develop severe jaundice requiring exchange transfusions but can remain anaemic for some weeks requiring "top-up" transfusions.

### Table 4: General plan of care for the timing and place of delivery for an antibody affected pregnancy

<table>
<thead>
<tr>
<th>ABs</th>
<th>IUT Yes/No</th>
<th>Delivery GA</th>
<th>Place of Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stable</td>
<td>No</td>
<td>37-38 weeks</td>
</tr>
<tr>
<td>2</td>
<td>Rising</td>
<td>No</td>
<td>Earlier than 37-38 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Rising</td>
<td>Yes</td>
<td>Delivery needs to be timed (fetus may be anaemic at birth). Decision depends GA of last IUT and rate of haemolysis and fetal Hb</td>
</tr>
</tbody>
</table>

Phototherapy is the first-line treatment for jaundice but if bilirubin levels continue to rise, exchange transfusion will be required. Some infants, especially those who have had multiple transfusions, may not develop severe jaundice requiring exchange transfusions but can remain anaemic for some weeks requiring "top-up" transfusions.

### Recurrence

The same intrauterine risk applies should the woman become pregnant again by the same 'genetic' (father) partner. The antibodies produced from the first pregnancy remain and repeat their destructive process if the subsequent fetus is Rh +ve. Women identified at the booking history as at risk, or those who are known to have a history of Rhesus disease must be referred to a fetal medicine specialist.

### Prevention

The 18th edition of the World Health Organisation Model List of Essential Medicines compendium includes the recommendation of anti-D immunoglobulin, under a section called ‘Sera and Immunoglobulins’. Since introducing anti-D as part of routine antenatal care and managing antibody affected pregnancies in the 1960s, mortality and morbidity rates have significantly reduced. Knowledge of and more widespread and routine use of anti-D provides the opportunity for more women and babies potentially affected to benefit. However, healthcare professionals need to be consistent in their practice to avoid unnecessary harm to the woman and her baby.

Recent data from SHOT - Serious Hazards of Transfusion reports that cumulative clinical and laboratory errors relating to anti-D use continue to occur due to lack of communication and adherence to guidelines. A key finding from these data is that most errors are late or missed prophylactic doses of anti-D immunoglobulin, putting women at risk. Most of these errors are made by midwives and nurses. Some errors were attributable to laboratory staff, but most were related to midwives and nurses. Errors described include: omission or late administration of anti-D; anti-D given to D positive women; anti-D given to women with immune anti-D; anti-D given to mother of D negative infant; anti-D given to the wrong woman; wrong dosage; anti-D given when expired, incorrect temperature or incorrectly labelled and failure of women returning for the injection if not readily available at their appointment.

Midwives are best placed to educate and inform women about the implications of red cell antibodies and how they and their unborn can benefit from prophylaxis as they are at forefront of midwifery care and a range of resources are available to enhance and support them in practice.

SHOT have produced an e-learning programme where midwives can access the ‘anti-D modules’ (www.learnbloodtransfusion.org.uk). A flowchart on the administration of anti-D Ig is also available which has been formally adopted by both BCSH and the RCOG.

In conclusion, with high quality education, training, resources and consistent approach to practice, all those involved in pregnancy care can better understand the use of anti-D and how this can benefit the woman and her pregnancy.
Further information

Several national organisations have produced information for healthcare professionals and the public about anti-D immunoglobulin and prenatal care.

Useful websites

http://www.bcsghguidelines.com
http://www.bmfms.org.uk
http://www.rhopylac.co.uk
http://www.rcm.org.uk
http://www.rcn.org.uk
https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg22/
http://www.shotuk.org
References


5. Royal College of Obstetricians and Gynaecologists (2010) Amniocentesis and Chorionic Villus Sampling Green-Top Guidelines No.8 RCOG June 2010


9. NICE Guidance TA156 (2008) Routine antenatal anti-D prophylaxis for women who are rhesus D negative


PRESCRIBING INFORMATION
(Please refer to the Summary of Product Characteristics before prescribing) Rhophylac® (human anti-D immunoglobulin) 300mcg (1500 IU)/2ml pre-filled syringe for injection. **Indications** Prevention of Rh(D) isoimmunisation in Rh(D) negative women. Treatment of Rh(D) negative adults, children and adolescents (0-18 years) after incompatible transfusions of Rh(D)-positive blood or other products containing red blood cells. **Dosage and administration** Prevention of Rh(D) immunisation in Rh(D) negative women: Planned antepartum prophylaxis: 300mcg (1500 IU) by intravenous (IV) or intramuscular (IM) injection between 28 and 30 weeks of gestation. Antepartum prophylaxis following complications of pregnancy: 300mcg as soon as possible and within 72 hours and repeated at 6-12 week intervals throughout the pregnancy if necessary. Postpartum prophylaxis: 300mcg (1500 IU) by IV or IM. If given IV a minimum dose of 200 mcg (1000 IU) may be sufficient provided large foeto-maternal haemorrhage (FMH) can be excluded. Administer as soon as possible within 72 hours of delivery. If more than 72 hours have elapsed, do not withhold but administer as soon as possible. If a large FMH is suspected, its extent should be determined and additional doses given. **Overweight patients:** In patients with a BMI ≥30 intravenous administration should be considered. Incompatible transfusions: 20mcg (100 IU) per 2 ml of transfused Rh(D)-positive blood or per 1 ml of red blood cell concentrate. The IV route is recommended. A maximum dose of 3000mcg (15,000 IU) is sufficient even if more than 300 ml of Rh(D)-positive blood or 150ml erythrocyte concentrate was infused. **Contraindications** Hypersensitivity to the active substance, any of the excipients or to human immunoglobulins. The intramuscular route in severe thrombocytopenia or other disorders of haemostasis. **Special warnings and special precautions for use** Rhophylac should not be given to the newborn infant. It is not intended for use in Rh(D) positive individuals or those already immunised to Rh(D) antigen. Allergic or anaphylactic type reactions can occur and warrant immediate discontinuation. Contains low levels of IgA. Individuals deficient in IgA have the potential for developing IgA antibodies and anaphylaxis. Monitor patients treated with very large doses for incompatible transfusions because of the risk of a haemolytic reaction. There have been reports that IM administration of Rhophylac in patients with a BMI ≥30 is associated with an increased risk of lack of effect. Therefore, in patients with a BMI ≥30 IV administration should be considered. Contains up to 11.5 mg (0.5 mmol) sodium per syringe. Despite standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma, the possibility of transmitting infective agents cannot be totally excluded. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV but may be of limited value against non-enveloped viruses such as HAV and parvovirus B19. The transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing. Efficacy of live vaccine immunisation may be impaired if given in close proximity to anti-D administration. **Undesirable effects** Hypersensitivity, anaphylactic shock, headache, tachycardia, hypotension, dyspnoea, nausea, vomiting, skin reaction, erythema, pruritus, arthralgia, fever, malaise, chills, injection site reaction. Severe intravascular haemolysis in Rh(D) positive primary immune thrombocytopenia (ITP) patients. Haemolysis resulting in death has been reported. **Marketing Authorisation Number:** PL 15036/0019 **Further information is available from:** CSL Behring UK Limited, Haywards Heath, West Sussex **Legal Category:** POM **Basic NHS Price:** £39.52 **Date text last revised:** 25 August 2016. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to CSL Behring UK Ltd. on 01444 447 405 UK/RHOP/16-0009