9.5: Prevention of haemolytic disease of the fetus and newborn (HDFN)

Pregnancies potentially affected by HDFN should be cared for by specialist teams with facilities for early diagnosis, intrauterine transfusion and support of high-dependency neonates.

HDFN occurs when the mother has IgG red cell alloantibodies in her plasma that cross the placenta and bind to fetal red cells possessing the corresponding antigen. Immune haemolysis may then cause variable degrees of fetal anaemia; in the most severe cases the fetus may die of heart failure in utero (hydrops fetalis). After delivery, affected babies may develop jaundice due to high unconjugated bilirubin levels and are at risk of neurological damage. The three most important red cell alloantibodies in clinical practice are to RhD (anti-D), Rhc (anti-c) and Kell (anti-K). The major effect of anti-K is suppression of red cell production in the fetus, rather than haemolysis.

Red cell alloantibodies in the mother occur as a result of previous pregnancies (where fetal red cells containing paternal blood group antigens cross the placenta) or blood transfusion. Naturally occurring IgG anti-A or anti-B antibodies in a group O mother can cross the placenta but rarely cause more than mild jaundice and anaemia in the neonate (ABO haemolytic disease). Recommendations for serological screening for maternal red cell antibodies in pregnancy are summarised in Table 9.1 (see also BCSH Guideline for Blood Grouping and Antibody Testing in Pregnancy – http://www.bcshguidelines.com). Knowledge of any maternal red cell alloantibodies is also important in providing compatible blood without delay in the event of obstetric haemorrhage.

Table 9.1 Screening for maternal red cell alloantibodies in pregnancy
At booking visit (12–16 weeks gestation) – maternal blood sample for ABO and Rh group and red cell alloantibody screen.

If an alloantibody capable of causing HDFN is detected (e.g. anti-D, c or K):

- Confirm in red cell reference laboratory, issue an Antibody Card to the mother and seek specialist clinical advice.
- Determining the father’s phenotype helps to predict the likelihood of a fetus carrying the relevant red cell antigen (but note issues around establishing paternity).
- The fetal genotype can now be determined by polymerase chain reaction on trace amounts of free fetal DNA in the mother’s circulation. This is currently highly sensitive for RhD, C, c, E, e and Kell.

Antenatal patients with anti-D, anti-c or anti-K should have regular repeat testing during the second trimester to monitor the antibody concentration:

- Usually every 4 weeks to 28 weeks gestation then every 2 weeks to term.
- Referral to a fetal medicine specialist is recommended once anti-D levels are >4 IU/mL, anti-c >7.5 IU/mL and in any woman with anti-K (as the severity of fetal anaemia is unpredictable).

All other women (both RhD positive and negative) should have repeat antibody screening at 28 weeks gestation (prior to RAADP) to exclude late development of red cell alloantibodies.

### 9.5.1: HDFN due to anti-D

This is the most important cause of HDFN and may occur in RhD negative women carrying a RhD positive fetus. Around 15% of white Europeans are RhD negative. Typically, the mother is sensitised by the transplacental passage of RhD positive fetal red cells during a previous pregnancy – usually at delivery or during the third trimester. HDFN then occurs in subsequent RhD positive pregnancies when further exposure to fetal red cells causes a secondary immune response and increased levels of maternal IgG anti-RhD alloantibodies that can cross the placenta. Before the introduction of routine postnatal prophylaxis with anti-RhD immunoglobulin (anti-D Ig, standard dose 500 IU) in the 1970s, HDFN was a major cause of perinatal mortality in the UK (46/100 000 births). Rates of sensitisation fell further with the introduction of routine antenatal anti-D prophylaxis in the third trimester (RAADP) and mortality is now <1.6/100 000 births.

### 9.5.2: Potentially sensitising events

RhD negative mothers can also produce anti-RhD in response to potentially sensitising events that may cause feto-maternal haemorrhage (FMH) during pregnancy or by blood transfusion. The BCSH Guideline for the Use of Anti-D Immunoglobulin for the Prevention of Haemolytic Disease of the Fetus and Newborn 2013 lists the following as potentially sensitising events in pregnancy:

- Amniocentesis, chorionic villus biopsy and cordocentesis
- Antepartum haemorrhage/vaginal bleeding in pregnancy
- External cephalic version
- Fall or abdominal trauma
- Ectopic pregnancy
- Evacuation of molar pregnancy
- Intrauterine death and stillbirth
- In utero therapeutic interventions (transfusion, surgery, insertion of shunts, laser)
- Miscarriage, threatened miscarriage
Therapeutic termination of pregnancy

Delivery – normal, instrumental or Caesarean section

Intraoperative cell salvage.

Recommendations for the administration of prophylactic anti-D Ig for potentially sensitising events are summarised in Table 9.2 and the reader is referred to the current BCSH Guideline for the Use of Anti-D Immunoglobulin for the Prevention of Haemolytic Disease of the Fetus and Newborn (http://www.bcsghguidelines.com) and the Royal College of Obstetricians and Gynaecologists’ Green Top Guideline No. 22 on the use of anti-D immunoglobulin for Rhesus D prophylaxis (http://www.rcog.org.uk/files/rcog-corp/GTG22AntiDJuly2013.pdf) for up-to-date guidance. An intramuscular (IM) injection of 125 IU anti-D Ig, or 100 IU of the appropriate preparation given intravenously (IV), ‘covers’ a FMH of 1 mL red cells. Women with anomalous RhD typing results should be treated as RhD negative until confirmatory testing is completed. Anti-D Ig should be administered within 72 hours of the potentially sensitising event (although some benefit may occur up to 10 days if treatment is inadvertently delayed).

If the pregnancy has reached 20 weeks or more, administration of anti-D Ig should be accompanied by a test on the mother’s blood to estimate the volume of fetal red cells that have entered the maternal circulation (e.g. Kleihauer test) in case it exceeds that covered by the standard dose of anti-D Ig. The Kleihauer test detects fetal cells, which contain HbF, in the maternal blood. If the screening Kleihauer test suggests a FMH >2 mL then the FMH volume should be confirmed by flow cytometry, which accurately measures the population of RhD positive cells. Detailed guidance is given in the 2009 BCSH Guidelines on the Estimation of Fetomaternal Haemorrhage (http://www.bcsghguidelines.com).

For recurrent or intermittent uterine bleeding, a minimum of 500 IU anti-D Ig should be given at 6-weekly intervals. Estimation of FMH haemorrhage by the Kleihauer technique should be carried out at 2-weekly intervals and additional anti-D Ig administered if required.

Table 9.2 Anti-D Ig for potentially sensitising events in pregnancy

<table>
<thead>
<tr>
<th>&lt;12 weeks</th>
<th>12–20 weeks</th>
<th>20+ weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 250 IU anti-D Ig if:</td>
<td>At least 250 IU anti-D Ig</td>
<td>At least 500 IU anti-D Ig</td>
</tr>
<tr>
<td>• surgical intervention</td>
<td>Kleihauer test not required</td>
<td>Take maternal blood for Kleihauer test</td>
</tr>
<tr>
<td>• termination of pregnancy (surgical or medical)</td>
<td></td>
<td>Further anti-D Ig if indicated by Kleihauer results</td>
</tr>
<tr>
<td>• unusually heavy bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• unusually severe pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• unsure of gestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kleihauer test not required</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9.5.3: Routine antenatal anti-D prophylaxis (RAADP)

RAADP should be offered to all RhD negative, non-sensitised women. They should be supplied with clear written information and informed consent should be obtained. Both two-dose (at 28 and 34 weeks) and larger single-dose (at 28–30 weeks) prophylactic anti-D regimens reduce maternal sensitisation but there are no comparative data to confirm their relative efficacy. The single-dose regimen may achieve better compliance but anti-D levels at term may be low in some women.
Recommended anti-D Ig doses for RAADP:

- Two-dose regimen – minimum of 500 IU at 28 and 34 weeks.

RAADP should be given even if the woman has received anti-D Ig prophylaxis for a potentially sensitising event earlier in the pregnancy. The transfusion laboratory should be informed of the administration of RAADP in case the woman requires pre-transfusion testing. It is not possible to differentiate between ‘prophylactic’ and ‘immune’ (allo-) anti-D in maternal blood in laboratory tests.

9.5.4: Anti-D Ig prophylaxis after the birth of a RhD positive baby or intrauterine death

Following the birth of a child to a RhD negative woman, a cord blood sample should be tested to determine the baby’s ABO and Rh group. If the cord Rh group is unclear, or if a sample cannot be obtained, the baby should be assumed to be RhD positive for anti-D Ig administration purposes. A direct antiglobulin test (DAT) on the cord sample should only be performed if HDFN is suspected.

If the baby is RhD positive, a minimum of 500 IU anti-D Ig should be administered to non-sensitised RhD negative women, within 72 hours of the birth.

A maternal blood sample for confirmation of her ABO and RhD status and for FMH screening should be taken within 2 hours of delivery. A dose of 500 IU anti-D Ig given IM will cover a FMH of up to 4 mL. If an additional dose is required, it should be based on 125 IU/mL fetal red cells if given IM or 100 IU/mL if given IV (manufacturer’s instructions on dosing should be followed and anti-D Ig produced for IM use only must not be given IV). If a FMH of >4 mL is detected, follow-up maternal blood samples should be tested 72 hours after an IM dose (48 hours if given IV) to confirm clearance of fetal red cells from the maternal circulation. In the case of very large FMH, administration of IV anti-D Ig may be more convenient and less painful than large-volume or repeated IM administration. If anti-D Ig is inadvertently omitted, there may be some benefit in giving prophylaxis up to 10 days.

If intraoperative cell salvage is used at Caesarean section, 1500 IU anti-D Ig should be administered immediately after the procedure if the baby is RhD positive and maternal FMH screening should be performed.

9.5.5: Inadvertent transfusion of RhD positive blood

If RhD positive blood is inadvertently transfused to a non-sensitised RhD negative woman of child-bearing potential, the advice of a transfusion medicine specialist should be obtained and the appropriate dose of anti-D Ig administered (125 IU/mL fetal red cells if given IM or 100 IU/mL IV). For transfusions >15 mL, IV anti-D Ig is more practical. FMH testing should be carried out at 48-hour intervals and further anti-D Ig given until clearance of fetal cells is confirmed. If more than one unit of red cells has been transfused, red cell exchange should be considered to reduce the load of RhD positive cells and the dose of anti-D Ig required.