Essentials

- Inappropriate transfusions during pregnancy and the postpartum period expose the mother to the risk of haemolytic disease of the fetus and newborn (HDFN) in subsequent pregnancies.
- Prevention and treatment of anaemia in pregnancy (most commonly due to iron deficiency) avoids unnecessary blood transfusion.
- A blood count should be checked at the antenatal booking visit and at 28 weeks (allowing sufficient time to treat iron deficiency before delivery).
- Oral iron replacement is appropriate for most patients, but intravenous iron (after the first trimester) may produce a more rapid response and should be used in women intolerant of oral iron.
- Transfusion is rarely required in haemodynamically stable pregnant women with Hb >70 or 80 g/L unless there is active (or a high risk of) bleeding.
- Cytomegalovirus (CMV) seronegative red cells should be provided for elective transfusions in pregnancy but standard, leucodepleted units may be used in an emergency to avoid delay.
- Major obstetric haemorrhage remains an important cause of maternal death. Successful management depends on well-rehearsed multidisciplinary protocols, rapid access to red cells (including emergency group O negative units) and excellent communication with the transfusion laboratory. Access to cell salvage reduces use of donor blood and early administration of tranexamic acid may reduce mortality.
- Pregnancies potentially affected by HDFN should be managed by specialist teams with facilities for early diagnosis, intrauterine transfusion and support of high-dependency neonates.
- Alloimmunisation of RhD negative women is the most important cause of HDFN. It was a major cause of perinatal mortality before routine postnatal anti-D Ig prophylaxis was introduced.
- Women may be alloimmunised by feto-maternal haemorrhage during pregnancy or at delivery, or by blood transfusion.
- Anti-D Ig should be administered within 72 hours of delivery of a RhD positive baby or a potentially sensitising event in pregnancy in accordance with national guidelines.
- The incidence of HDFN has been further reduced by the addition of routine antenatal anti-D prophylaxis (RAADP).

9.1: Normal haematological values in pregnancy

During normal pregnancy, physiological changes in the mother affect the reference range for haematological parameters. Knowledge of these changes helps to avoid unnecessary blood transfusions caused by misinterpretation of blood count results:

- Maternal plasma volume increases by around 50% above the non-pregnant value by the late second trimester. Red cell mass only increases by 25–30%, resulting in a fall in Hb concentration ('physiological anaemia of pregnancy').
• Up to 10% of healthy pregnant women have a count below the non-pregnant reference range of 150–400×10⁹/L at term (‘gestational thrombocytopenia’). The count rarely falls below 100×10⁹/L and there is no increase in bleeding risk.
• Many coagulation factors, including plasma fibrinogen and Factor VIIIc, are increased in normal pregnancy and the anticoagulant factor Protein S is reduced. This contributes to the increased risk of thrombotic complications in pregnancy.

9.2: Anaemia and pregnancy

Prevention of anaemia in pregnancy is important in avoiding unnecessary blood transfusion. The World Health Organization (WHO) defines anaemia in pregnant women as Hb <110 g/L and postpartum anaemia as Hb <100 g/L. Taking account of the physiological changes in Hb concentration during pregnancy, the 2011 British Committee for Standards in Haematology (BCSH) UK Guidelines on the Management of Iron Deficiency in Pregnancy (https://b-s-h.org.uk/) recommend the following thresholds for investigation of anaemia:

- First trimester: Hb <110 g/L
- Second and third trimesters: Hb <105 g/L
- Postpartum: Hb <100 g/L.

9.2.1: Iron deficiency

This is the most common cause of anaemia in pregnancy. At least 30% of UK women have absent iron stores at the onset of pregnancy due to menstrual bleeding and suboptimal dietary intake. Babies born to iron-deficient mothers are more likely to be anaemic in the first 3 months of life and have a higher risk of abnormal psychomotor development. Severe maternal iron deficiency, common in less developed countries, may cause increased risk of preterm delivery and low birth weight. Iron-deficient mothers often have increased fatigue, poor concentration and emotional disturbance. After delivery, this may impair the ability to look after the newborn and prevent successful initiation of breastfeeding.

A routine full blood count should be carried out at the antenatal booking visit and at 28 weeks (allowing sufficient time to treat iron deficiency before delivery). Serum ferritin levels <15 µg/L are diagnostic of absent iron stores and a level <30 µg/L should prompt iron supplementation.

9.2.1.1: Treatment of iron deficiency anaemia in pregnancy

Dietary changes are not sufficient to correct iron deficiency in pregnancy. Oral iron supplements are the first choice, with a therapeutic dose of 100 to 200 mg elemental iron daily (e.g. ferrous sulphate or ferrous fumarate 200 mg two or three times daily). The Hb concentration should increase by around 20 g/L over 3 to 4 weeks and iron should be continued for 3 months after the Hb returns to normal (and at least 6 weeks postpartum) to replenish iron stores.

Many women are intolerant of oral iron because of gastric irritation and diarrhoea or constipation. If a reduction in oral iron dose is not effective, then treatment with parenteral iron should be considered. Modern intravenous iron preparations (see Chapter 6) are safe after the first trimester and may produce a faster and more complete response than oral iron. They are particularly useful when anaemia is diagnosed late in pregnancy. The ability to give a single total replacement dose makes it possible to treat postpartum iron deficiency anaemia before the mother leaves hospital.

9.2.2: Folate deficiency
Anaemia due to folate deficiency is less common and usually reflects poor dietary intake of fresh fruit and leafy vegetables. Other causes include malabsorption (most commonly coeliac disease) or increased requirements in haemolytic anaemia or haemoglobinopathies. Folate deficiency typically produces a macrocytic anaemia (large red blood cells – increased mean cell volume (MCV) on full blood count). Treatment is with oral folic acid 5 mg daily.

### 9.3: Red cell transfusion in pregnancy

Clinical audits show that many transfusions in pregnancy, especially in the postpartum period, are inappropriate and could be prevented by better antenatal monitoring and the targeted use of iron supplements. Transfusion exposes women to the risk of sensitisation to red cell antigens and haemolytic disease of the fetus and newborn (HDFN) in subsequent pregnancies. In the absence of major haemorrhage, the decision to transfuse should be made after careful clinical assessment rather than on the basis of a specific Hb concentration. Clinically stable, healthy women with Hb >70 or 80 g/L can usually be managed with oral or parenteral iron. Transfusion should be reserved for women with continued bleeding (or at risk of further significant haemorrhage), severe symptoms that need immediate correction or evidence of cardiac decompensation.

Obstetric units should have agreed local guidelines for red cell transfusion in women who are not actively bleeding. Cytomegalovirus (CMV) seronegative red cells should be provided, where possible, for pregnant women. In an emergency, such as major haemorrhage, standard leucocyte-depleted components should be given to avoid delay.

### 9.4: Major obstetric haemorrhage

Blood flow to the uterus is around 700 mL/minute at term and bleeding can be dramatic and rapidly fatal. Risk factors for obstetric haemorrhage include placenta praevia, placental abruption and postpartum haemorrhage (most commonly due to uterine atony). Obstetric haemorrhage is a major problem in less developed countries, responsible for half of the approximately 500 000 maternal deaths each year across the world. Major haemorrhage remains an important cause of maternal mortality in the UK, with an incidence of 3.7 per 1000 births and nine deaths in 2006–2008. Analysis by the UK Centre for Maternal and Child Enquiries (CMACE) (http://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2010.02847.x/pdf) shows that the management of fatal cases was often suboptimal with underestimation of the degree of haemorrhage and poor team working. The Centre emphasises the need for:

- Clear local policies
- Training of front-line staff
- Multidisciplinary team working
- Regular ‘fire drills’
- Excellent communication with the blood transfusion laboratory.

Obstetric haemorrhage is often complicated by disseminated intravascular coagulation (DIC) and defibrination. The primary treatment is evacuation of the uterine contents but supportive therapy with fresh frozen plasma (FFP), cryoprecipitate (or fibrinogen concentrate) and platelet transfusion is often required. There is increasing evidence that the antifibrinolytic agent, tranexamic acid, can significantly reduce mortality in major obstetric haemorrhage and this is being explored in a large international randomised trial (the WOMAN trial – [http://www.thewomantrial.lshtm.ac.uk/](http://www.thewomantrial.lshtm.ac.uk/)).

The Royal College of Obstetricians and Gynaecologists has produced guidelines on the prevention and management of postpartum haemorrhage ([http://www.rcog.org.uk/womens-health/clinical-guidance](http://www.rcog.org.uk/womens-health/clinical-guidance)).
Obstetric and anaesthetic staff of appropriate seniority must be involved and access to expert haematological advice is important. Transfusion support for patients with major obstetric haemorrhage should follow the basic principles discussed in Chapter 7. There must be rapid access to compatible red cells and blood components, including emergency group O RhD negative blood. Use of intraoperative cell salvage (ICS) by teams experienced in the technique reduces exposure to donor red cells and can be life-saving, especially in women who decline allogeneic blood transfusion. Use of ICS in obstetrics is endorsed by the National Institute for Health and Care Excellence (NICE). Salvaged blood should be transfused through a leucodepletion filter (see Chapter 6).

The dose of tranexamic acid used in the WOMAN trial is 1g by intravenous injection as soon as possible; a second dose is given if bleeding persists after 30 minutes or recurs within the first 24 hours.

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>
<thead>
<tr>
<th>Table 9.1 Screening for maternal red cell alloantibodies in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>At booking visit (12–16 weeks gestation) – maternal blood sample for ABO and Rh group and red cell alloantibody screen.</td>
</tr>
<tr>
<td>If an alloantibody capable of causing HDFN is detected (e.g. anti-D, c or K):</td>
</tr>
<tr>
<td>• Confirm in red cell reference laboratory, issue an Antibody Card to the mother and seek specialist clinical advice.</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>Antenatal patients with anti-D, anti-c or anti-K should have regular repeat testing during the second trimester to monitor the antibody concentration:</td>
</tr>
<tr>
<td>• Usually every 4 weeks to 28 weeks gestation then every 2 weeks to term.</td>
</tr>
</tbody>
</table>
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.bcshguidelines.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 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.