Royal College of Obstetricians & Gynaecologists

The Management of Women with Red Cell Antibodies during Pregnancy

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The Management of Women with Red Cell Antibodies during Pregnancy

This is the first edition of this guideline.

Executive summary of recommendations

Prepregnancy counselling

Women with red cell antibodies, particularly if there is a risk of fetal anaemia or if compatible donor red cells for transfusion may be difficult to obtain, should attend for prepregnancy counselling with a clinician with knowledge and expertise of this condition. ✓

Red cell antibodies in pregnancy

What red cell antibodies are clinically significant (maternal and fetal) during pregnancy?

All women should have their blood group and antibody status determined at booking and at 28 weeks of gestation (Appendix 2). D

What are the implications for the fetus and neonate from red cell antibodies?

Clinicians should be aware that severe fetal anaemia can result in hydrops which significantly worsens the perinatal outcome. D

When and how should paternal and fetal genotyping be performed?

Non-invasive fetal genotyping using maternal blood is now possible for D, C, c, E, e and K antigens. This should be performed in the first instance for the relevant antigen when maternal red cell antibodies are present. C

For other antigens, invasive testing (chorionic villus sampling [CVS] or amniocentesis) may be considered if fetal anaemia is a concern or if invasive testing is performed for another reason (e.g. karyotyping). ✓

Is karyotyping contraindicated in the presence of maternal red cell antibodies?

Invasive testing is not contraindicated if alloimmunisation has occurred. ✓

Anti-D prophylaxis should be given to cover invasive testing if the mother is rhesus D (RhD) negative and is not sensitised. D

If the fetus is at risk of anaemia, when should referral to a fetal medicine specialist take place?

Referral to a fetal medicine specialist should occur when there are rising antibody levels/titres, a level/titre above a specific threshold (see section 6.7) or ultrasound features suggestive of fetal anaemia. ✓

Referral should take place if there is a history of unexplained severe neonatal jaundice, neonatal anaemia requiring transfusion or exchange transfusion, in order to exclude haemolytic disease of the fetus and newborn (HDFN) as the cause. ✓

For antibodies other than anti-D, anti-c and anti-K, the following should prompt referral to a fetal medicine specialist: a history of previous significant HDFN or intrauterine transfusion (IUT), or a titre of 32 or above, especially if the titre is rising as rising titres correlate with increasing risk and severity of anaemia. D

What thresholds should be used for the various antibodies that could cause fetal anaemia to trigger referral for further investigation or monitoring?

An anti-D level of > 4 iu/ml but < 15 iu/ml correlates with a moderate risk of HDFN and an anti-D level of > 15 iu/ml can cause severe HDFN. Referral for a fetal medicine opinion should therefore be made once anti-D levels are > 4 iu/ml. C

An anti-c level of > 7.5 iu/ml but < 20 iu/ml correlates with a moderate risk of HDFN, whereas an anti-c level of > 20 iu/ml correlates with a high risk of HDFN. Referral for a fetal medicine opinion should therefore be made once anti-c levels are > 7.5 iu/ml. C

For anti-K antibodies, referral should take place once detected, as severe fetal anaemia can occur even with low titres. ✓

The presence of anti-E potentiates the severity of fetal anaemia due to anti-c antibodies so that referral at lower levels/titres is indicated (unless the fetus has only one of these antigens). ✓

Once detected how often should antibody levels be monitored during pregnancy?

Anti-D and anti-c levels should be measured every 4 weeks up to 28 weeks of gestation and then every 2 weeks until delivery. D

Although anti-K titres do not correlate well with either the development or severity of fetal anaemia, titres should nevertheless be measured every 4 weeks up to 28 weeks of gestation, then every 2 weeks until delivery. D

For all other antibodies, retesting at 28 weeks is advised with the exception of women who have a previous history of pregnancies affected with HDFN when early referral to a fetal medicine specialist is also recommended. ✓

For antibodies that could potentially cause problems with cross-matching or issues with the availability of appropriate blood, discussion with the blood transfusion service is required regarding the frequency of antenatal testing. This may depend on the type of antibody as well as the likelihood of requiring blood at short notice. ✓

How should pregnancies at risk of fetal anaemia be monitored?

The cause of the alloimmunisation, relevant past history and pregnancy outcomes should be ascertained in order to generate an assessment of risk of HDFN. ✓

If the fetus carries the corresponding antigen for a maternal antibody which is capable of causing fetal anaemia and if the antibody levels/titres rise beyond the levels detailed in section 6.7 then the pregnancy should be monitored weekly by ultrasound, specifically assessing the fetal middle cerebral artery peak systolic velocities (MCA PSV). B

Referral to a fetal medicine specialist for consideration of invasive treatment should take place if the MCA PSV rises above the 1.5 multiples of the median (MoM) threshold or if there are other signs of fetal anaemia. ✓

Fetal monitoring is required (as above) once anti-K is detected. ✓

If fetal transfusion is required what type of donor blood should be used?

Red cell preparations for IUT should be group O (low titre haemolysin) or ABO identical with the fetus (if known) and negative for the antigen(s) corresponding to maternal red cell antibodies. D

IUTs should be performed only in fetal medicine units that have the requisite invasive skills and appropriate perinatal haematology expertise. ✓

What are the implications for the mother from red cell antibodies?

For antibodies other than anti-D, anti-c, anti-C, anti-E or anti-K, maternity staff should liaise with their local transfusion laboratory to assess and plan for any possible transfusion requirements, as obtaining the relevant blood may take longer. ✓

How often should pregnant women with red cell antibodies who are at high risk of requiring a transfusion (placenta praevia, sickle cell disease etc.) be tested?

Pregnant women with red cell antibodies, who are assessed as being at high risk of requiring a blood transfusion, should have a cross-match sample taken at least every week. ✓

If maternal transfusion is required, what type of donor blood or blood components should be used?

Red cell components of the same ABO group and RhD type, and that are K negative and cytomegalovirus (CMV) negative, should be selected. D

Should RhD-negative women who have anti-D or non-anti-D antibodies receive routine antenatal or postnatal prophylaxis?

Anti-D immunoglobulin should be given to RhD-negative women with non-anti-D antibodies for routine antenatal prophylaxis, for potential antenatal sensitising events and postnatal prophylaxis. B

If immune anti-D is detected, prophylaxis is no longer necessary. D

Discussion and liaison with the transfusion laboratory are essential in determining whether anti-D antibodies are immune or passive in women who have previously received anti-D prophylaxis. D

Requirements for blood

What are the logistics of obtaining blood or blood components for the woman, fetus or neonate?

Blood or blood components for the woman.

Close collaboration between the maternity, neonatology and haematology staff is essential. ✓

When blood is required for women with multiple antibodies or antibodies against high prevalence antigens, planning is required as rare blood donors may need to be called up to donate, or frozen blood may need to be obtained from the National Frozen Blood Bank in Liverpool. ✓

Local blood transport time and time for cross-match should be taken into account when the decision for transfusion is made. ✓

Blood for intrauterine transfusion (IUT)

Clinicians should be aware that blood for IUT has the same requirements as blood for neonatal exchange (see 7.1.3), except that plasma is removed by the blood centre to increase the haematocrit to 0.70–0.85 and it is always irradiated. D

Blood for neonatal exchange

Blood should be ABO compatible with the neonate and mother (to avoid ABO HDFN from the woman's anti-A or -B antibodies present), RhD negative (or RhD identical with neonate), K negative, negative for the corresponding antigen to which the woman has an antibody and cross-match compatible with the woman's blood sample. D

Blood should be less than 5 days old (to ensure low supernatant potassium levels), CMV negative and irradiated unless the risk to the baby of delaying exchange transfusion while obtaining irradiated blood outweighs this. It should be plasma reduced (rather than in saline-adenine-glucose-mannitol [SAGM] additive solution), with a haematocrit of 0.50–0.60. D

Blood for neonatal small volume ('top-up') transfusion

Blood should be ABO compatible with the neonate and mother (to avoid ABO HDFN from the woman's anti-A or -B antibodies present), RhD negative (or RhD identical with neonate), K negative and negative for the corresponding antigen to which the woman has an antibody and cross-match compatible with the woman's blood sample. D

Blood should be CMV negative but does not need to be irradiated unless the neonate has had a previous IUT and blood can be stored in SAGM (rather than plasma reduced) and be up to 35 days old (as a top-up transfusion is a much smaller volume than an exchange transfusion). D

Clinicians considering transfusion in a neonate must check if the baby has had an IUT, as if so, blood must be irradiated to prevent transfusion-associated graft-versus-host disease. D

What blood or blood components can be administered in the emergency situation to a woman known to have red cell antibodies?

The decision to use ABO-, RhD- and K-compatible blood that is not matched for other antibodies (or O negative, where the woman's ABO and RhD groups are unknown) should be made on the balance of risks (severe haemorrhage versus a haemolytic transfusion reaction). ✓

Transfusion should not be delayed in the event of life-threatening haemorrhage. Close liaison with the transfusion laboratory is essential. ✓

Birth

What is the optimum mode, place and timing of birth?

Timing of delivery for women with red cell antibodies that can cause fetal anaemia will depend on the antibody levels/titres, rate of rise as well as if any fetal therapy has been required. The mode, timing and place of delivery are otherwise dependent on standard obstetric grounds. ✓

If a woman is at risk of requiring significant amounts of transfused blood either antenatally, intrapartum or postnatally, consideration should be given to transferring her care to a centre capable of processing cross-match samples and providing appropriate compatible blood rapidly. ✓

As these are 'high-risk' pregnancies, continuous electronic fetal heart monitoring is advised during labour. ✓

Cord blood investigations

What cord blood investigations should be performed?

If a woman has clinically significant antibodies (Appendix 1) then cord samples should be taken for a direct antiglobulin test (DAT), haemoglobin and bilirubin levels. ✓

Management

How should the neonate be managed?

This depends on the risk of haemolysis or anaemia conferred by the relevant red cell antibody. The neonate should have regular clinical assessment of its neurobehavioural state and be observed for the development of jaundice and/or anaemia. C

Regular assessment of bilirubin and haemoglobin levels should be made and early discharge is not advisable. ✓

The mother should be encouraged to feed the baby regularly to guard against dehydration, since dehydration can increase the severity of jaundice. ✓

Clinicians should be aware that if bilirubin levels rise rapidly or above the interventional threshold, phototherapy and/or exchange transfusion may be required. C

Pregnancies complicated by red cell alloimmunisation with a minimal or no risk of fetal or neonatal anaemia require no specific treatment. ✓

Future Risks

What is the risk of recurrence in a future pregnancy?

A woman with a history of a pregnancy or infant affected by HDFN should be referred for early assessment to a fetal medicine specialist in all further pregnancies. ✓

Long-term consequences of red cell antibodies to women and their offspring

What are the long-term health consequences for the woman?

Women can be advised that there are no long-term adverse health consequences associated with the presence of red cell antibodies. ✓

What are the long-term health concerns for the children of women with red cell antibodies during pregnancy?

Clinicians should be aware that some infants may experience anaemia persisting for a few weeks following birth. C

Clinicians should be aware that some infants may develop late anaemia which is usually due to hyporegenerative anaemia. C

1. Purpose and scope

The purpose of this guideline is to provide guidance on the management of pregnant women with red cell antibodies predating the pregnancy or those developing antibodies during pregnancy. The guideline also includes the management of fetal anaemia caused by red cell antibodies, as well as the early management of the neonate at risk of anaemia and/or hyperbilirubinaemia. It does not address the management of the pregnant woman with anti-platelet antibodies or other autoimmune or alloimmune antibodies.

2. Introduction and background epidemiology

The presence of maternal red cell antibodies during pregnancy is a relatively common finding and requires close collaboration between the blood transfusion laboratory, obstetric and neonatal care providers. A population study from the Netherlands found that red cell antibodies were detected in 1.2% of pregnancies, while the prevalence of clinically significant antibodies was placed at 0.4% (Appendix 1).[1]

The presence of red cell antibodies signifies alloimmunisation that has occurred as a result of previous pregnancy, transfusion or transplantation. Haemolytic disease of the fetus and newborn (HDFN) is a condition in which transplacental passage of maternal immunoglobulin G (IgG) antibodies results in immune haemolysis of fetal/neonatal red cells. Some antibodies (including anti-D, anti-K (-Kell) and anti-c) confer significant fetal and neonatal risks such as anaemia requiring intrauterine or neonatal transfusion, jaundice or perinatal loss. There are many antibodies that are unlikely to significantly affect the fetus but can cause neonatal anaemia and hyperbilirubinaemia, while others may cause problems for the screening and provision of appropriate blood or blood components to the mother or fetus/neonate when required (Appendix 1).

Anti-D is the most commonly encountered antibody during pregnancy. Before routine antenatal anti-D prophylaxis, late immunisation during a first pregnancy was responsible for 18–27% of cases. Immunisation during a second or subsequent pregnancy probably accounts for a similar proportion of cases, although it is often impossible to distinguish late sensitisation from failure of prophylaxis at the end of the preceding pregnancy.[2] Antibodies of the ABO blood group system can also cause mild to moderate anaemia and jaundice in the neonate and occasionally in the fetus. In particular, anti-A and anti-B antibodies of the IgG subclass in a group O mother can cross the placenta and cause haemolysis of fetal erythrocytes.

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews), DARE, EMBASE, TRIP, MEDLINE and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews, meta-analyses and other studies. The search was restricted to articles published between 1960 and July 2013. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search terms included: red cell antibody, red blood cell antigen, erythroblastosis fetalis, blood group incompatibility, haemolytic disease of newborn, anti-D, anti-c, anti-E, anti-K, Kidd, Duffy, Diego alloimmunisation. The search was limited to humans and the English language. NHS Evidence and the National Guideline Clearinghouse were also searched for relevant guidelines and reviews.

4. Prepregnancy counselling

4.1 Is prepregnancy counselling necessary for women known to have red cell antibodies prior to pregnancy?

Women with red cell antibodies, particularly if there is a risk of fetal anaemia or if compatible donor red cells for transfusion may be difficult to obtain, should attend for prepregnancy counselling with a clinician with knowledge and expertise of this condition. ✓

Routine prepregnancy screening for red cell antibodies is not indicated. Most women would have had antibodies detected in a previous pregnancy, screening prior to blood transfusion/donation or fortuitously for some other indication. Women with clinically significant red cell antibodies should be given information regarding the possible implications (maternal and fetal) to the pregnancy. This will clearly depend on the type of antibody present. Counselling should be by a clinician with knowledge and expertise of this condition and in most cases this will be a fetal medicine specialist.

A guideline issued by the British Committee for Standards in Haematology (BCSH)[3] on antibodies in pregnancy recommends that women with clinically significant antibodies should be issued with a card giving details of the antibody.

5. Assisted reproductive techniques (ART)

5.1 Do assisted reproductive techniques (ART) increase the risk of red cell antibodies developing?

There is no evidence that ART increases the risk of red cell alloimmunisation. However, if donor eggs are used for a mother with an alloantibody and the donor red cell antigen status is not known, fetal genotyping may be required.

6. Red cell antibodies in pregnancy

6.1 What is the incidence of red cell antibodies in pregnancy?

In a population study conducted in the Netherlands, the prevalence of positive antibody screens was 1:80, with a 1:300 prevalence of clinically significant alloantibodies other than anti-D.[1]

Evidence level 2++

Previous blood transfusion is an important cause for alloimmunisation with antibodies other than anti-D implicated in HDFN.[4]

Evidence level 2+

6.2 What red cell antibodies are clinically significant (maternal and fetal) during pregnancy?

All women should have their blood group and antibody status determined at booking and at 28 weeks of gestation (Appendix 2).

D

Relevant antibodies are presented in Appendix 1. Antibodies to many of the red cell antigens have the potential to be clinically significant and will have implications for the selection of blood for transfusion in the mother to avoid the risk of haemolytic transfusion reactions (HTRs). For this reason, the blood group and antibody status of the mother should be tested at booking and at 28 weeks of gestation.[5] In addition to the risk of fetal anaemia, the presence of maternal red cell antibodies can hinder the timely provision of blood and blood components because of difficulty in obtaining antigen-negative blood and/or cross-matching issues.[3]

Evidence level 4

The risk of fetal anaemia is greatest with anti-D, anti-c and anti-K antibodies. Other antibodies that potentially cause significant fetal anaemia include anti-E, -Fy^a, -Jk^a, -C and -Ce.[6–9] There are numerous other antibodies that usually only cause mild haemolysis that is only rarely significant (Appendix 1).

Evidence level 3

6.3 What are the implications for the fetus and neonate from red cell antibodies?

Clinicians should be aware that severe fetal anaemia can result in hydrops which significantly worsens the perinatal outcome.

D

Fetal anaemia, hyperbilirubinaemia and neonatal jaundice can result from red cell antibodies that cause haemolysis or impaired erythropoiesis in utero. Untreated, severe fetal anaemia can result in hydrops, preterm birth or perinatal death. The overall perinatal survival in pregnancies complicated

Evidence level 3

by red cell antibodies causing fetal anaemia following treatment was reported to be 84%, with nonhydropic fetuses having better survival (94%) than hydropic fetuses (74%).[10]

Evidence level 3

Anti-K causes anaemia secondary to erythroid suppression and immune destruction of early erythroid progenitor cells, but hyperbilirubinaemia is not a prominent feature.[11] Severe fetal anaemia can occur even at relatively low antibody titres.[12]

Evidence level 2+

6.4 When and how should paternal and fetal genotyping be performed?

Non-invasive fetal genotyping using maternal blood is now possible for D, C, c, E, e and K antigens. This should be performed in the first instance for the relevant antigen when maternal red cell antibodies are present.

C

For other antigens, invasive testing (chorionic villus sampling [CVS] or amniocentesis) may be considered if fetal anaemia is a concern or if invasive testing is performed for another reason (e.g. karyotyping).

✓

Where clinically significant maternal red cell antibodies are detected, the paternal phenotype can be ascertained by serology. However with the rhesus D (RhD) antigen specifically, in an antigen-positive father, while a likely phenotype can be deduced, genotyping is required to determine whether he is homozygous or heterozygous for the *RHD* gene. If the father is homozygous for the red cell antigen then all pregnancies are potentially at risk.

It is also reasonable to omit paternal testing and proceed directly to fetal genotyping to avoid issues of nonpaternity. It is now possible to determine the fetal genotype non-invasively from maternal blood.[13] Using polymerase chain reaction techniques, the fetal *RHD* status can be detected with great sensitivity using free fetal DNA (ffDNA) extracted from maternal plasma. The fetal C, c, E, e and K genotype can also be detected using this method (with an accuracy of fetal RhC/c and RhE/e genotype estimations from maternal blood between 96–98%, which compares well with the reported accuracy of fetal RhD of > 95%).[14,15] Genotyping can be undertaken from 16 weeks of gestation for all except K which can be undertaken from 20 weeks, due to the risk of a false-negative result if performed earlier in pregnancy. However, in some cases, results are inconclusive as it is not possible to confirm that fetal DNA, as well as maternal DNA, is present in the sample. In these cases, consideration may need to be given to repeating the non-invasive test, performing an amniocentesis or managing the pregnancy as one that is at risk. It is also reasonable not to perform fetal genotyping until the antibody reaches a level that would warrant fetal middle cerebral artery (MCA) Doppler monitoring.

Evidence level 2+

Of note, in dizygotic twins, a maternal blood test for fetal genotyping will not differentiate between the twins: just that at least one has the corresponding gene. If fetal monitoring for anaemia is indicated, each twin would need to be monitored separately.

Non-invasive genotyping is not possible for some red cell antigens. In these cases invasive testing (CVS or amniocentesis) may be considered. However, the risks of the procedure (miscarriage, worsening of alloimmunisation) need to be balanced against the benefit that knowledge of the fetal genotype brings to the management of the pregnancy. It would normally only be indicated if there was a history of a significant problem with HDFN, or MCA Doppler ultrasound suggested developing fetal anaemia and intrauterine transfusion (IUT) was being considered.

6.5 Is karyotyping contraindicated in the presence of maternal red cell antibodies?

Invasive testing is not contraindicated if alloimmunisation has occurred.

✓

Anti-D prophylaxis should be given to cover invasive testing if the mother is RhD negative and is not sensitised.

D

Invasive testing solely for the purposes of fetal genotyping is seldom required as this can be undertaken using maternal blood in the majority of cases. However, if karyotyping is necessary for a separate indication, concomitant genotyping can be performed.

In addition to the procedure-related risks, any invasive procedure will further increase the risk of alloimmunisation, through either the increasing of antibody levels or the development of further antibodies. If the mother is RhD negative and is not sensitised, anti-D prophylaxis should be given to cover invasive testing.[16]

Evidence level 4

6.6 If the fetus is at risk of anaemia, when should referral to a fetal medicine specialist take place?

Referral to a fetal medicine specialist should occur when there are rising antibody levels/titres, a level/titre above a specific threshold (see section 6.7) or ultrasound features suggestive of fetal anaemia. ✓

Referral should take place if there is a history of unexplained severe neonatal jaundice, neonatal anaemia requiring transfusion or exchange transfusion, in order to exclude HDFN as the cause. ✓

For antibodies other than anti-D, anti-c and anti-K, the following should prompt referral to a fetal medicine specialist: a history of previous significant HDFN or IUT, or a titre of 32 or above, especially if the titre is rising as rising titres correlate with increasing risk and severity of anaemia. D

Referral to a fetal medicine specialist will depend on the type of antibody and its levels or titres. The risk of fetal anaemia is greatest with anti-D, anti-c and anti-K. In addition to these antibodies, other antibodies may rarely cause fetal anaemia (Appendix 1) and referral may be indicated.[1,3] Once alloimmunisation has occurred, the fetus may be at risk from anaemia and the risk appears to correlate with increasing antibody titres.

Evidence level 4

6.7 What thresholds should be used for the various antibodies that could cause fetal anaemia to trigger referral for further investigation or monitoring?

An anti-D level of > 4 iu/ml but < 15 iu/ml correlates with a moderate risk of HDFN and an anti-D level of > 15 iu/ml can cause severe HDFN. Referral for a fetal medicine opinion should therefore be made once anti-D levels are > 4 iu/ml. C

An anti-c level of > 7.5 iu/ml but < 20 iu/ml correlates with a moderate risk of HDFN, whereas an anti-c level of > 20 iu/ml correlates with a high risk of HDFN. Referral for a fetal medicine opinion should therefore be made once anti-c levels are > 7.5 iu/ml. C

For anti-K antibodies, referral should take place once detected, as severe fetal anaemia can occur even with low titres. ✓

The presence of anti-E potentiates the severity of fetal anaemia due to anti-c antibodies so that referral at lower levels/titres is indicated (unless the fetus has only one of these antigens). ✓

An anti-D level < 4 iu/ml or an anti-c level of < 7.5 iu/ml correlates with a low risk of fetal anaemia and therefore referral to a fetal medicine specialist is not immediately indicated (Appendix 3).[3,17,18] Serial monitoring of antibody levels is necessary. Once referral to a fetal medicine specialist has been made for assessment of pregnancy at moderate or high risk of HDFN, the value of subsequent quantitation of anti-D and anti-c levels is doubtful. Further testing is however required at 28 weeks for the development of additional red cell antibodies. Caution is required however if there is a history of a severely affected previous pregnancy even if the antibody levels are low in the current pregnancy. For such cases early referral to a fetal medicine specialist should be made so that an

Evidence level 2+

expert assessment of risk can be undertaken. For these women, ultrasound monitoring may be required even with low antibody levels.

Evidence level 2+

Anti-K titres appear to correlate poorly with the severity of disease with fetal anaemia occurring at titres as low as 8.[19]

The presence of anti-E potentiates the severity of fetal anaemia due to anti-c antibodies so, unless the fetus has only one of these antigens, referral at lower levels/titres is indicated.

6.8 Once detected how often should antibody levels be monitored during pregnancy?

Anti-D and anti-c levels should be measured every 4 weeks up to 28 weeks of gestation and then every 2 weeks until delivery. D

Although anti-K titres do not correlate well with either the development or severity of fetal anaemia, titres should nevertheless be measured every 4 weeks up to 28 weeks of gestation, then every 2 weeks until delivery. D

For all other antibodies, retesting at 28 weeks is advised with the exception of women who have a previous history of pregnancies affected with HDFN when early referral to a fetal medicine specialist is also recommended. ✓

For antibodies that could potentially cause problems with cross-matching or issues with the availability of appropriate blood, discussion with the blood transfusion service is required regarding the frequency of antenatal testing. This may depend on the type of antibody as well as the likelihood of requiring blood at short notice. ✓

Blood samples from women with immune anti-D, anti-c or anti-K should be tested at least monthly until 28 weeks of gestation and every 2 weeks thereafter until delivery to monitor the level of antibody and to identify any additional antibodies that may have developed.[3]

When red cell antibodies are detected in the 'booking' sample, further testing of maternal blood should be undertaken to determine the specificity and level of antibody or antibodies, and to assess the likelihood of HDFN.[3] The levels of anti-D and anti-c antibodies are quantified using an automated analyser whereas the titre of other antibodies is determined by titration using doubling dilution.

Evidence level 4

6.9 How should pregnancies at risk of fetal anaemia be monitored?

The cause of the alloimmunisation, relevant past history and pregnancy outcomes should be ascertained in order to generate an assessment of risk of HDFN. ✓

If the fetus carries the corresponding antigen for a maternal antibody which is capable of causing fetal anaemia and if the antibody levels/titres rise beyond the levels detailed in section 6.7 then the pregnancy should be monitored weekly by ultrasound, specifically assessing the fetal middle cerebral artery peak systolic velocities (MCA PSV). B

Referral to a fetal medicine specialist for consideration of invasive treatment should take place if the MCA PSV rises above the 1.5 multiples of the median (MoM) threshold or if there are other signs of fetal anaemia. ✓

Fetal monitoring is required (as above) once anti-K is detected. ✓

The cause of the alloimmunisation should be ascertained: for example, inadequate or omitted anti-D prophylaxis or a previous blood transfusion. Details of previously affected pregnancies, particularly IUTs and the gestation at which they were commenced, neonatal anaemia, gestation at delivery and the need for exchange transfusions or phototherapy, should also be obtained. This information enables a risk assessment of the pregnancy to be made. Ultrasound monitoring should commence once there is a moderate or severe risk of fetal anaemia.[20]

Evidence level 2+

If the fetus is antigen positive, it will be at risk of anaemia and the pregnancy needs to be serially monitored. Pregnancies at risk should be monitored on a weekly basis looking specifically at the MCA PSV. Other signs that might suggest fetal anaemia include polyhydramnios, skin oedema and cardiomegaly. Although the risks of fetal anaemia are well known for anti-D, anti-c and anti-K antibodies and weekly monitoring is advisable, the risks for other less common antibodies is difficult to precisely quantify. A reasonable approach would be ultrasound monitoring every 1–2 weeks using the MCA PSV.

Ultrasound monitoring should be performed by a professional with appropriate expertise to reliably perform MCA Doppler assessment (see International Society of Ultrasound in Obstetrics and Gynecology practice guidelines for the use of Doppler ultrasonography in obstetrics[21]). If the MCA PSV rises beyond the interventional threshold then referral to a fetal medicine specialist with expertise in IUT should be made.

MCA PSV monitoring is predictive of moderate or severe fetal anaemia with 100% sensitivity and a false positive rate of 12%.[20]

Evidence level 2+

If monitoring of the MCA indicates anaemia (MCA PSV > 1.5 MoM), fetal blood sampling (FBS) and possibly IUT are indicated. Monitoring with MCA PSV should be used with caution after 36 weeks as its sensitivity for the detection of fetal anaemia decreases. If there are concerns beyond this gestation because of raised MCA PSV, further advice should be sought from a fetal medicine specialist experienced in managing fetal anaemia. Further management should also be discussed with a fetal medicine specialist if MCA PSV levels are normal despite high or increasing antibody levels beyond 36 weeks of gestation. The risk of fetal loss following an FBS is 1–3%, but is higher if the fetus is hydropic.[10]

The procedure is carried out under continuous ultrasound guidance with facilities for immediate analysis of the fetal blood haemoglobin and haematocrit. The risks and benefits of IUT should always be discussed with the woman who should be made aware of the consequences of untreated severe fetal anaemia (i.e. hydrops, preterm birth, perinatal death, severe neonatal jaundice and kernicterus) as well as the risks of neonatal exchange transfusion.

6.10 If fetal transfusion is required what type of donor blood should be used?

Red cell preparations for IUT should be group O (low titre haemolysin) or ABO identical with the fetus (if known) and negative for the antigen(s) corresponding to maternal red cell antibodies. D

IUTs should be performed only in fetal medicine units that have the requisite invasive skills and appropriate perinatal haematology expertise. ✓

Blood should be IAT (indirect antiglobulin test) cross-match compatible with maternal plasma and negative for the relevant antigen(s) determined by maternal antibody status.[22] K-negative blood is recommended to reduce additional maternal alloimmunisation risks. It should also be less than 5 days old and in citrate phosphate dextrose (CPD) anticoagulant, cytomegalovirus (CMV) seronegative, irradiated and transfused within 24 hours of irradiation. Blood packs should have a haematocrit (packed cell volume, PCV) of 0.70–0.85.[23] Blood for IUT should never be transfused straight from 4°C storage.[22] In exceptional cases, it will be necessary to give O RhD-positive, c-negative blood, for example in HDFN because of anti-c alloimmunisation, where giving RhD-negative blood would be harmful.[22]

Evidence level 4

As the number of cases of fetal anaemia due to red cell alloimmunisation is decreasing, fewer fetal medicine specialists will have the necessary skills to perform IUTs. These cases should be referred to tertiary units where the appropriate intrauterine invasive skills and perinatal haematology expertise are available. If FBS is being performed for suspected fetal anaemia, the appropriate blood pack for an IUT should be immediately available. This will require prior liaison with the transfusion laboratory. It is not good practice to perform a diagnostic FBS and then defer the IUT to a later time because suitable blood is not available.

While 24 hours' notice may be requested for planned IUTs, in an emergency, blood for IUT can be provided in less time following discussion with the blood transfusion service; in a dire emergency, discussion should be undertaken with the relevant consultant haematologist regarding the best compromise of blood available.

6.11 What are the implications for the mother from red cell antibodies?

For antibodies other than anti-D, anti-c, anti-C, anti-E or anti-K, maternity staff should liaise with their local transfusion laboratory to assess and plan for any possible transfusion requirements, as obtaining the relevant blood may take longer. ✓

The implications relate to possible transfusion problems for the mother in terms of the availability and provision of compatible blood.

6.12 How often should pregnant women with red cell antibodies who are at high risk of requiring a transfusion (placenta praevia, sickle cell disease etc.) be tested?

Pregnant women with red cell antibodies, who are assessed as being at high risk of requiring a blood transfusion, should have a cross-match sample taken at least every week. ✓

Current BCSH guidelines require a sample no more than 72 hours old for providing compatible blood in pregnancy,[24] but do allow a deviation to the 3-day rule for individual cases such as high-risk women with placenta praevia without red cell antibodies where weekly samples can be taken, as long as a risk assessment is made and recorded in each individual case. In high-risk women with red cell antibodies where a sample every 72 hours is not feasible, a sample should be taken once a week and if transfusion is required a new sample should be taken immediately, to exclude new antibody development. However, in the event of life-threatening haemorrhage, urgent transfusion should not be delayed (see section 7.2) and close liaison with the hospital transfusion laboratory is vital.

6.13 If maternal transfusion is required, what type of donor blood or blood components should be used?

Red cell components of the same ABO group and RhD type, and that are K negative and CMV negative, should be selected. D

If group ABO-identical blood is not available for group A, B or AB patients, group O blood should be used. Pregnant women and women of childbearing age who are RhD negative should receive RhD-negative blood. The transfused blood should also be K negative. Blood which has been phenotyped and found negative for the antigen corresponding to the maternal antibody should be provided. Antigen-negative red cells should also be selected when a clinically significant antibody has previously been identified, but cannot be detected in the most recent cross-match sample. An IAT cross-match must be used if the woman's plasma contains or has previously contained clinically significant red cell alloantibodies (see section 7.2).[24] For planned antenatal transfusions, CMV-negative blood should be transfused.[25] Screening for CMV should not delay transfusion in an emergency situation; all blood in the UK also undergoes leucodepletion which significantly reduces risk of CMV transmission by blood.[25]

Evidence level 4

6.14 Should RhD-negative women who have anti-D or non-anti-D antibodies receive routine antenatal or postnatal prophylaxis?

Anti-D immunoglobulin should be given to RhD-negative women with non-anti-D antibodies for routine antenatal prophylaxis, for potential antenatal sensitising events and postnatal prophylaxis. B

If immune anti-D is detected, prophylaxis is no longer necessary. D

Discussion and liaison with the transfusion laboratory are essential in determining whether anti-D antibodies are immune or passive in women who have previously received anti-D prophylaxis. D

Anti-D immunoglobulin prophylaxis is given to prevent RhD-negative women forming anti-D antibodies in the event of a potentially sensitising event during pregnancy and/or as part of routine antenatal anti-D prophylaxis (RAADP).[16,26] It is important to remember to administer anti-D prophylaxis to RhD-negative women who have other red cell antibodies, as this will still prevent the formation of immune anti-D. Evidence level 2++

Women who are already sensitised, i.e. have immune anti-D, should not be given anti-D prophylaxis.[3] Evidence level 4

In the non-RhD-sensitised woman, if fetal genotyping indicates that the fetus is RhD negative or if the father is confirmed to be RhD negative then anti-D prophylaxis is not required.

Women given anti-D immunoglobulin may have a positive antibody screen on subsequent testing and it may be difficult to determine if this anti-D is passive following administration of a prophylactic dose or immune as result of sensitisation. It is essential to liaise with the transfusion laboratory to discuss appropriate interpretation.[3] Evidence level 4

7. Requirements for blood

7.1 What are the logistics of obtaining blood or blood components for the woman, fetus or neonate?

7.1.1 Blood or blood components for the woman

Close collaboration between the maternity, neonatology and haematology staff is essential. ✓

When blood is required for women with multiple antibodies or antibodies against high prevalence antigens, planning is required as rare blood donors may need to be called up to donate, or frozen blood may need to be obtained from the National Frozen Blood Bank in Liverpool. ✓

Local blood transport time and time for cross-match should be taken into account when the decision for transfusion is made. ✓

An assessment and discussion of the likelihood of the need for blood, as well as all appropriate preventative measures to reduce the likelihood of transfusion should take place as early in pregnancy as feasible between the maternity and haematology staff. This will optimise the use of rare blood, taking account of the needs of the patient together with the scarcity of the blood. Any haematinic deficiency should be corrected. Multidisciplinary planning of delivery should take place to reduce blood loss and intra-operative cell salvage should be available where appropriate.

The appropriate management of transfusion in the mother and the baby requires essential communication not only between teams within a hospital but also between hospitals if cases are referred to tertiary centres.

Blood can usually be sourced from hospital stocks for women with anti-D, -c, -C, -E or -K as all units are labelled

with full Rh and K antigen status. For antibodies other than anti-D, -c, -C, -E and -K, blood will most likely need to be obtained from the regional blood transfusion centre, so additional transport time may be required. For antibodies where compatible blood is rare, a national search for compatible blood may be required. If insufficient blood is available, blood may need to be obtained from the National Frozen Blood Bank in Liverpool, or rare blood donors called up to donate. Obtaining frozen blood entails a delay of approximately 4–6 hours for 2 units to be thawed, multiply washed and processed to remove glycerol, with a further 2 hours for each additional 2 units plus additional transportation time.

The shelf life of frozen units, once thawed, is 72 hours and they cannot be refrozen. Calling up rare donors to donate requires advance notification where possible. There may be additional delays because of necessary virology testing and other processing which may take up to 1 working day. The timing of obtaining appropriate donor blood should take account of when the woman is most likely to need that blood.

7.1.2 Blood for intrauterine transfusion (IUT)

Clinicians should be aware that blood for IUT has the same requirements as blood for neonatal exchange (see 7.1.3), except that plasma is removed by the blood centre to increase the haematocrit to 0.70–0.85 and it is always irradiated. D

Blood for IUT is processed to order as it only has 24 hours' shelf life after processing and normally requires a minimum of 1 working day's notice, unless an emergency.[22,23] As with neonatal exchange blood, if maternal antibodies other than anti-D, -c, -C, -E or -K are present, advance warning should be given where possible to ensure that suitable blood, negative for all relevant antigens, is available. Evidence level 4

7.1.3 Blood for neonatal exchange

Blood should be ABO compatible with the neonate and mother (to avoid ABO HDFN from the woman's anti-A or -B antibodies present), RhD negative (or RhD identical with neonate), K negative, negative for the corresponding antigen to which the woman has an antibody and cross-match compatible with the woman's blood sample. D

Blood should be less than 5 days old (to ensure low supernatant potassium levels), CMV negative and irradiated unless the risk to the baby of delaying exchange transfusion while obtaining irradiated blood outweighs this. It should be plasma reduced (rather than in saline-adenine-glucose-mannitol [SAGM] additive solution), with a haematocrit of 0.50–0.60. D

If maternal antibodies other than anti-D, -c, -C, -E or -K are present, units negative for those antigens may require a search of other centres. Ideally, in view of the 5-day shelf life, staff should discuss such cases with the blood transfusion laboratory in advance of delivery to ensure that appropriate blood is available. Once irradiated, exchange blood has a shelf life of 24 hours.[22]

Blood should be CMV negative, to minimise the risk of CMV infection in the neonate and irradiated to prevent transfusion-associated graft-versus-host disease, due to the large volume of blood transfused to a neonate. Plasma-reduced blood is preferable as blood suspended in SAGM contains glucose, which can result in rebound hypoglycaemia, and mannitol with potential diuretic and intracerebral pressure effects. The recommended haematocrit allows for sufficient correction of anaemia after exchange, but without an unacceptably high haematocrit, with its associated risks to the neonate.[22] Evidence level 4

Blood for exchange transfusion is normally obtained from a regional blood centre, which routinely stocks groups O negative and O positive (c negative and K negative) exchange units on the shelf. Blood transport time and time for cross-match should also be taken into account.

7.1.4 Blood for neonatal small volume ('top-up') transfusion

Blood should be ABO compatible with the neonate and mother (to avoid ABO HDFN from the woman's anti-A or -B antibodies present), RhD negative (or RhD identical with neonate), K negative and negative for the corresponding antigen to which the woman has an antibody and cross-match compatible with the woman's blood sample.

D

Blood should be CMV negative but does not need to be irradiated unless the neonate has had a previous IUT and blood can be stored in SAGM (rather than plasma reduced) and be up to 35 days old (as a top-up transfusion is a much smaller volume than an exchange transfusion).

D

Clinicians considering transfusion in a neonate must check if the baby has had an IUT, as if so, blood must be irradiated to prevent transfusion-associated graft-versus-host disease.

D

While blood for IUT should be irradiated because of the physiological immune incompetence of the fetus allowing transfusion-induced tolerance or immunosuppression, for top-up (small volume) neonatal transfusions, in the absence of any preceding IUT, irradiation is not required.[22]

Evidence level 4

In view of the less restrictive shelf life of blood required, blood compatible for maternal antibodies other than anti-D, -c, -C, -E or -K may be more readily available in the regional blood centre than blood for exchange or IUT, but advance warning should be given to transfusion labs wherever possible.

7.2 What blood or blood components can be administered in the emergency situation to a woman known to have red cell antibodies?

The decision to use ABO-, RhD- and K-compatible blood that is not matched for other antibodies (or O negative, where the woman's ABO and RhD groups are unknown) should be made on the balance of risks (severe haemorrhage versus a haemolytic transfusion reaction).

✓

Transfusion should not be delayed in the event of life-threatening haemorrhage. Close liaison with the transfusion laboratory is essential.

✓

Obstetric, haematology and transfusion laboratory staff should discuss when to give alternative blood, when sufficient compatible blood is not readily available, based on the balance of clinical risks (severe haemorrhage versus a haemolytic transfusion reaction with associated complications, including renal failure).

If ABO-, RhD- and K-compatible blood that is not matched for other antibodies is used for resuscitation in the event of life-threatening haemorrhage, consider giving intravenous methylprednisolone 1 g and monitor the woman closely.[27] If a severe transfusion reaction develops, full resuscitative measures, including the use of adrenaline, may be required.[28] The presence of maternal red cell antibodies has no implications for other blood components such as platelets, fresh frozen plasma, cryoprecipitate or fractionated products.

Evidence level 4

8. Birth

8.1 What is the optimum mode, place and timing of birth?

Timing of delivery for women with red cell antibodies that can cause fetal anaemia will depend on the antibody levels/titres, rate of rise as well as if any fetal therapy has been required. The mode, timing and place of delivery are otherwise dependent on standard obstetric grounds.

✓

If a woman is at risk of requiring significant amounts of transfused blood either antenatally, intrapartum or postnatally, consideration should be given to transferring her care to a centre capable of processing cross-match samples and providing appropriate compatible blood rapidly. ✓

As these are 'high-risk' pregnancies, continuous electronic fetal heart monitoring is advised during labour. ✓

In general, for red cell antibodies that could cause fetal anaemia but which have been stable throughout pregnancy, delivery should take place between 37 and 38 weeks of gestation. If an IUT has not been required but antibody levels are rising then consideration for earlier delivery may be necessary. If an IUT has been required, delivery will need to be timed to ensure that the fetus is not significantly anaemic at birth. This will depend on the gestation that the last IUT was performed as well as the estimated rate of drop of fetal haemoglobin/haematocrit. Decisions about the timing of delivery are most appropriately made by the fetal medicine team managing these pregnancies. Prior IUT is not in itself an indication for elective caesarean section. The neonatal team should be advised of the timing of delivery in the event that further neonatal care is required.

As not all obstetric units will have the haematological expertise and resources to deal with cases of massive obstetric haemorrhage against the background of difficulties in obtaining blood safe for transfusion, consideration should be given to transferring these more complex cases to a centre where such facilities are available.

Although the National Institute for Health and Care Excellence (NICE) guideline on intrapartum care contains no specific recommendation for fetal monitoring in pregnancies complicated by red cell antibodies,[29] these pregnancies are generally considered to be 'high risk' and intrapartum continuous electronic fetal heart monitoring is therefore advised.

9. Cord blood investigations

9.1 What cord blood investigations should be performed?

If a woman has clinically significant antibodies (Appendix 1) then cord samples should be taken for a direct antiglobulin test (DAT), haemoglobin and bilirubin levels. ✓

Cord blood investigations (DAT, haemoglobin and bilirubin levels) should be undertaken in addition to ABO and RhD typing where the mother is known to have immune red cell antibodies. A positive DAT indicates that the infant's red cells are coated with antibody but in itself cannot predict severity of haemolysis. Notably the DAT may be negative in ABO HDFN. It is therefore essential to also determine haemoglobin and bilirubin levels to ascertain the degree of anaemia and haemolysis at birth and this helps guide management as below.

10. Management

10.1 How should the neonate be managed?

This depends on the risk of haemolysis or anaemia conferred by the relevant red cell antibody. The neonate should have regular clinical assessment of its neurobehavioural state and be observed for the development of jaundice and/or anaemia. C

Regular assessment of bilirubin and haemoglobin levels should be made and early discharge is not advisable. ✓

The mother should be encouraged to feed the baby regularly to guard against dehydration, since dehydration can increase the severity of jaundice. ✓

Clinicians should be aware that if bilirubin levels rise rapidly or above the interventional threshold, phototherapy and/or exchange transfusion may be required. C

Pregnancies complicated by red cell alloimmunisation with a minimal or no risk of fetal or neonatal anaemia require no specific treatment. ✓

Guidance from NICE[30] summarises the approach to the management of neonatal jaundice including bilirubin and haemoglobin monitoring, indications for phototherapy, intravenous immunoglobulin use and exchange transfusion. Exchange transfusion may be used to manage severe anaemia at birth and to treat severe hyperbilirubinaemia. Such a transfusion is undertaken with the aims of removing both the antibody-coated red cells and the excess bilirubin.[22]

Evidence level 2+/2++

11. Future risks

11.1 What is the risk of recurrence in a future pregnancy?

A woman with a history of a pregnancy or infant affected by HDFN should be referred for early assessment to a fetal medicine specialist in all further pregnancies. ✓

The risk of recurrence of HDFN depends on the type of antibody, the paternal genotype as well as the severity and gestational onset of the fetal anaemia.

12. Long-term consequences of red cell antibodies to women and their offspring

12.1 What are the long-term health consequences for the woman?

Women can be advised that there are no long-term adverse health consequences associated with the presence of red cell antibodies. ✓

There are no long-term health consequences for the woman, but an antibody card should be carried in case transfusion is required.[31]

Evidence level 2–

12.2 What are the long-term health concerns for the children of women with red cell antibodies during pregnancy?

Clinicians should be aware that some infants may experience anaemia persisting for a few weeks following birth. C

Clinicians should be aware that some infants may develop late anaemia which is usually due to hyporegenerative anaemia. C

Anaemia persisting for a few weeks after birth is usually the result of passively acquired maternal antibodies causing continued haemolysis.[32]

Late anaemia may develop due to a transient suppression of neonatal erythropoiesis, itself due to transfusion. Babies who have required several IUTs are at particular risk.[32]

Evidence level 2+

Affected infants have suppression of erythropoiesis with low numbers of reticulocytes despite a low packed cell volume and normal erythropoietin values. 'Top-up' transfusions are required only if the infant is symptomatic. There is some evidence that the need and frequency of 'top-up' transfusions may be decreased if recombinant erythropoietin is used.[33–35]

The risk of long-term neurodevelopmental delay is no different in the antenatally treated cohort compared with unaffected pregnancies, with normal outcome expected in more than 90% of cases.[36] With appropriate management, kernicterus is seen rarely. Sensorineural hearing loss is more common in infants affected by haemolytic disease of the newborn because of the toxic effect of prolonged exposure of bilirubin on the developing eighth cranial nerve.

13. Recommendations for future research

Studies[37,38] using maternally administered intravenous immunoglobulin have demonstrated some benefit in severe cases of RhD incompatibility but the precise mechanism of action is not established. This treatment modality is appropriate only in selected cases and it may prolong the time interval before the first intrauterine treatment is required. Further studies are required.

The use of intravenous immunoglobulin administered to the infant to reduce the severity of hyperbilirubinaemia and the number of exchange transfusions also needs further validation in larger studies.

14. Auditable topics

- Pregnancy outcomes of women referred for antenatal fetal therapy for fetal anaemia.
- Proportion of women referred to a fetal medicine specialist once their antibody level/titre has reached an interventional threshold.
- Outcomes of women with rare/unusual antibodies requiring blood or blood components during pregnancy or in the puerperium.
- Outcomes of neonates requiring phototherapy or transfusion (exchange or top-up) because of haemolysis secondary to red cell alloimmunisation.
- Confirmation of the accuracy of free fetal DNA tests as basic quality assurance for laboratories undertaking such tests.

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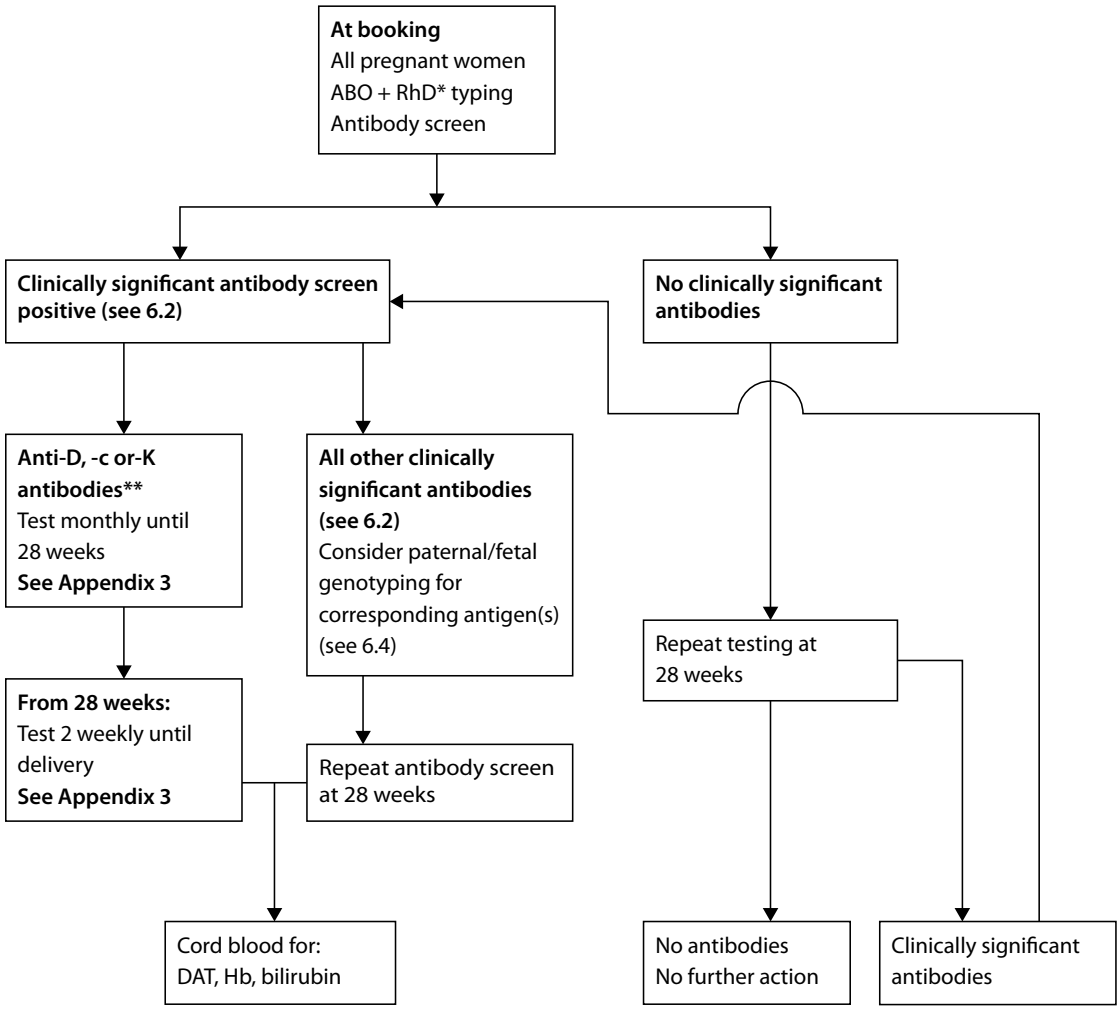
Appendix I: Red cell antibodies showing published clinical significance

Antibody	HDFN	Haemolytic transfusion reaction
D	Severe in fetus and neonate	Severe
c	Severe in fetus and neonate	Severe
K	Severe in fetus and neonate	Severe
c+E	Severe in fetus and neonate*	Severe
E	Yes in neonate*[39,40]	Yes
C	Yes in neonate*	Yes
e	Yes in neonate	Yes
Ce	Yes in neonate	Yes
Fy^a	Yes in neonate*[6]	Yes
Fy^b	Yes in neonate	Yes
Fy^3	No	Yes
Jk^a	Yes in neonate*	Yes
Jk^b	No	Yes
S	Yes in neonate	Yes
s	Yes in neonate	Yes
U	Yes in neonate*	Yes
M	Yes (occasionally)*[41]	Yes (if active at 37°C)
N	Mild (1 case)	Yes
H (Bombay)	Yes in neonate*	Yes
G	Yes in neonate	Yes
k	Yes in neonate*[42]	Yes
Kp^a	Yes (in neonate occasionally)	No
C^w	Yes (in neonate occasionally)	No
Vel	No	Yes

Anti-D, -c and -K are the three main antibodies that have been reported to cause severe anaemia, jaundice or death in the fetus or neonate. Many other antibodies (*) can cause anaemia or jaundice predominantly in the neonatal period but there have also been occasional case reports of the **fetus** being severely affected.

The antibodies listed in the table above are the most common, clinically significant antibodies. Other rarer antibodies can cause HDFN and haemolytic transfusion reactions occasionally. For further advice, discussion with the transfusion laboratory and/or consultant haematologist would be beneficial.

Appendix II: Timing and frequency of antibody screening in pregnancy

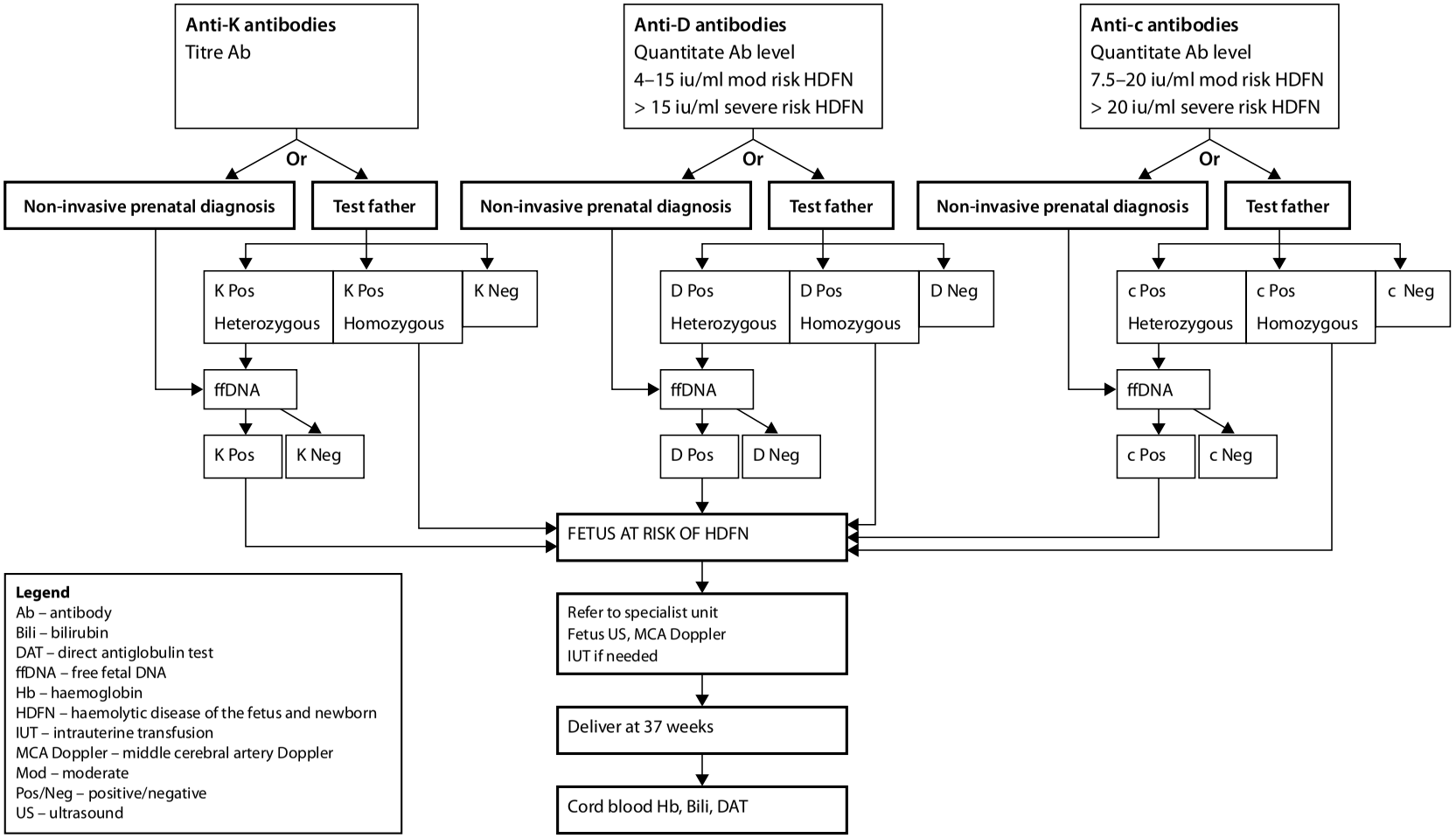


* If RhD-negative mother with no immune anti-D antibodies then advise anti-D prophylaxis for any potentially sensitising events in pregnancy and give routine antenatal anti-D prophylaxis either RAADP single dose or two doses (see RCOG anti-D guidelines); after delivery check cord sample for RhD type and maternal sample for fetomaternal haemorrhage (e.g. Kleihauer) testing to check if further anti-D needed in addition to the standard dose which should be given in the first instance after delivery.

** Pregnancies with immune anti-D, -K or -c are at particular risk of severe fetal HDFN so further early assessment and referral to fetal medicine specialist is indicated (see 6.7).

Legend
DAT – direct antiglobulin test; Hb – haemoglobin; RAADP – routine antenatal anti-D prophylaxis

Appendix III: Management algorithm for pregnancies complicated with anti-D, anti-K or anti-c alloimmunisation



Appendix IV: List of abbreviations

ART	assisted reproductive techniques
BCSH	British Committee for Standards in Haematology
CMV	cytomegalovirus
CPD	citrate phosphate dextrose
DAT	direct antiglobulin test
FBS	fetal blood sampling
ffDNA	free fetal DNA
HDFN	haemolytic disease of the fetus and newborn
HTR	haemolytic transfusion reaction
IAT	indirect antiglobulin test
IgG	immunoglobulin G
IUT	intrauterine transfusion
MCA PSV	middle cerebral artery peak systolic velocities
MoM	multiples of the median
NICE	National Institute for Health and Care Excellence
PCV	packed cell volume
RAADP	routine antenatal anti-D prophylaxis
RhD	rhesus D
SAGM	saline-adenine-glucose-mannitol

Appendix V: Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in 'Clinical Governance Advice No.1 *Development of RCOG Green-top Guidelines'* (available on the RCOG website at http://www.rcog.org.uk/files/rcog-corp/CGA1dConsensusMethods.pdf). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated. The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The review process will commence in 2017, unless otherwise indicated.

