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The Use of Anti-D Immunoglobulin for Rhesus D Prophylaxis

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This is the third edition of this guideline, which was originally published in 1998 and revised in 2002 under the same title.

1. Background and introduction

The development of anti-D antibodies usually occurs as a result of fetomaternal haemorrhage (FMH) in a rhesus D (RhD)-negative woman with an RhD-positive fetus. Post-delivery immunoprophylaxis using anti-D immunoglobulin (anti-D Ig) began in the UK in 1969. The programme has been an astounding success: deaths attributed to RhD alloimmunisation fell from 46/100 000 births before 1969 to 1.6/100 000 in 1990.[1]

The recommendations in this edition of the guideline are taken from the updated review of the National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance 156[2] and from the Health Technology Assessment on routine antenatal anti-D prophylaxis (RAADP) for rhesus-negative women.[3]

Guidelines on RhD immunoprophylaxis were updated in 1976,[4] 1981[5] and 1991.[6] However, RhD alloimmunisation continues to occur. There is clear evidence that the 1991 guidelines are not being fully applied.[7,8] However, the most important cause of anti-D antibodies is now immunisation during pregnancy where there has been no overt sensitising event. Late immunisation, during the third trimester of a first pregnancy, is responsible for 18–27% of cases. Immunisation during a second or subsequent pregnancy probably accounts for a similar proportion of cases, although in this situation it is impossible to distinguish late sensitisation from failure of prophylaxis at the end of the preceding pregnancy.[9]

The recommendations in the 2002 RCOG Green-top Guideline of the same title were taken directly from the guidelines drawn up by a joint working group of the British Blood Transfusion Society and the RCOG.[10]

This guideline refers to the management of the non-sensitised RhD-negative woman.

2. 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 and meta-analyses. The search was restricted to articles published between 1999 and February 2010. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search words included 'Rho (D) immune globulin', 'Rh isoimmunization', 'isoantibodies', 'rhesus disease', 'Rh D haemolytic disease', 'erythroblastosis fetalis', 'Rho (D) antigen', 'RHO (D) antibody', 'anti D', 'dose, dosage', 'pregnancy', 'drug toxicity', and 'anti D, reaction', and the search was limited to humans and the English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews.

3. Test for the size of FMH

3.1 How should the size of FMH be quantified?

A Kleihauer screening test should be performed within 2 hours of delivery to identify RhD-negative women with a large FMH who require additional anti-D Ig. D

Studies have shown that approximately 99% of women have an FMH of less than 4 ml at delivery. Of the cases where the FMH is greater than 4 ml, 50% will have occurred during normal delivery.[11] However, the following clinical circumstances are more likely to be associated with a large FMH:[12]

- traumatic deliveries including caesarean section
- manual removal of the placenta
- stillbirths and fetal deaths
- abdominal trauma during the third trimester
- twin pregnancies (at delivery)
- unexplained hydrops fetalis.

Evidence level 3/4

In the UK, testing to quantify the size of FMH is recommended. The same is true in the USA, Canada, France and Ireland, although not in most European countries. The test usually undertaken in the UK is the Kleihauer acid elution test, which detects fetal haemoglobin.

The recommended policy in the UK is to obtain an anticoagulated blood sample as soon as possible (within 2 hours) after delivery and to undertake a Kleihauer screening test to identify women with a large FMH who need additional anti-D Ig. In some European countries (exceptions include the UK, France and Ireland), a standard postnatal dose of 1000–1500 iu is used with no requirement for a routine Kleihauer test.[13] Unfortunately, this policy does not take account of the fact that up to 0.3% of women have an FMH greater than 15 ml which will not be covered by 1500 iu of anti-D Ig. Hence, if the 1500 iu dose is implemented without a test to quantitate FMH, over 200 women each year in the UK would receive less protection than they do now. Where there is not the facility to perform Kleihauer testing to quantify the FMH at delivery, it is reasonable to administer a standard postnatal dose of 1500 iu anti-D Ig.

However, it is recognised that in some remote areas in the UK and in UK military units there is not the facility to perform Kleihauer testing to quantify the FMH at delivery. In this situation it is reasonable to administer a standard postnatal dose of 1500 iu anti-D Ig.

Flow cytometry offers an alternative technique for quantifying the size of FMH.[14] Flow cytometry has a number of advantages in that results are more accurate and more reproducible than those from the Kleihauer test and that it detects RhD-positive cells, making it particularly helpful in women with high fetal haemoglobin levels. Not all hospitals will have ready access to a flow cytometer, although several blood centres offer to estimate FMH. Flow cytometry is probably most effectively employed in those cases where a Kleihauer screening test indicates a large FMH which requires accurate quantitation and follow-up. The rosetting technique is a relatively simple serological method which offers another alternative for quantifying FMH of RhD-positive red cells greater than 4 ml.

4. Anti-D Ig preparations licensed for use in the UK[10]

4.1 Which anti-D Ig preparations are available for use in the UK?

Anti-D Ig is a blood product extracted from the plasma of donors who have high circulating levels of anti-D, usually resulting from deliberate immunisation of Rh-negative donors. The following preparations, which are obtained from US donors, are available in the UK:

- D-GAM® (Bio Products Laboratory, Elstree, UK): 250 iu, 500 iu, 1500 iu and 2500 iu vials for intramuscular use only
- Partobulin SDF (Baxter BioScience, Thetford, UK): 1250 iu prefilled syringe for intramuscular use only
- Rhophylac® (CSL Behring, Haywards Heath, UK): 1500 iu prefilled syringe for intramuscular or intravenous use
- WinRho SDF® (Baxter BioScience): 1500 and 5000 IU vials for intramuscular or intravenous use (in the UK this product is used solely for the treatment of idiopathic thrombocytopenic purpura).

4.2 What dose of anti-D Ig should be administered?

An intramuscular dose of 500 iu of anti-D Ig will neutralise an FMH of up to 4 ml. For each millilitre of FMH in excess of 4 ml, a further 125 micrograms of anti-D Ig is necessary. Minimum recommended doses of anti-D Ig at less than 20^{+0} weeks of gestation and at 20^{+0} weeks of gestation and above are 250 iu and 500 iu, respectively. As a result of the varying prefilled syringe doses available for the different anti-D Ig products, the actual dose given will depend on the product used in individual maternity units and may be higher than is clinically necessary.

The only source of therapeutic anti-D Ig is human plasma. There have been concerns about the risk of viral and prion transmission. Donors undergo specific virology testing and the end product is subject to a viral inactivation process. The excellent safety record of intramuscular immunoglobulins predates the introduction of these additional measures.[15]

5. Administration

5.1 How should anti-D Ig be administered?

For successful immunoprophylaxis, anti-D Ig should be given as soon as possible after the potentially sensitising event but always within 72 hours. If it is not given before 72 hours, every effort should still be made to administer the anti-D Ig, as a dose given within 10 days may provide some protection. D

Ideally, anti-D Ig should be administered into the deltoid muscle. ✓

Women who have a bleeding disorder should receive anti-D Ig via the subcutaneous or intravenous route. ✓

Consent should be obtained and recorded in the case notes. ✓

Women who are already sensitised to RhD should not be given anti-D Ig. Intramuscular anti-D Ig is best given into the deltoid muscle as injections into the gluteal region often only reach the subcutaneous tissues and absorption may be delayed.

Intramuscular injections should not be given to women with bleeding disorders. If required, anti-D Ig should be administered subcutaneously (D-GAM, Partobulin SDF) or intravenously (Rophylac, WinRho SDF).

Women who have a weak expression of the RhD blood group (Du) do not form anti-D and therefore do not require prophylaxis. It should be noted that anti-D Ig does not protect against the development of other antibodies which can cause haemolytic disease of the newborn.

6. Prophylaxis following miscarriage, ectopic pregnancy and termination of pregnancy

6.1 When is anti-D Ig prophylaxis required following miscarriage, ectopic pregnancy and termination of pregnancy?

When indicated, anti-D Ig is administered in a dose of 250 iu up to 19^{+6} weeks of gestation and in a dose of 500 iu thereafter. A test for the size of FMH should be performed when anti-D Ig is given at or after 20^{+0} weeks of gestation.

6.1.1 Miscarriage

Anti-D Ig should be given to all non-sensitised RhD-negative women who have a spontaneous complete or incomplete miscarriage at or after 12^{+0} weeks of gestation. D

Anti-D Ig is not required for spontaneous miscarriage before 12^{+0} weeks of gestation, provided there is no instrumentation of the uterus. D

Anti-D Ig should be given to non-sensitised RhD-negative women undergoing surgical evacuation of the uterus, regardless of gestation. D

Anti-D Ig should be considered for non-sensitised RhD-negative women undergoing medical evacuation of the uterus, regardless of gestation. D

Anti-D Ig should be given to all non-sensitised RhD-negative women who have a spontaneous complete or incomplete miscarriage after 12^{+0} weeks of gestation. Published data on which to base recommendations for earlier miscarriages are scant. There is evidence that significant FMH occurs only after curettage to remove products of conception but does not occur after complete spontaneous miscarriages.[16,17] Anti-D Ig should therefore be given when there has been an intervention to evacuate the uterus. Medically induced evacuation of the uterus with prostaglandins is likely to result in increased uterine contractions and bleeding compared with spontaneous miscarriage. There is a lack of evidence to guide the use of anti-D Ig for medical evacuation of the uterus but it seems reasonable to consider anti-D administration in this situation. By contrast, the risk of immunisation by spontaneous miscarriage before 12^{+0} weeks of gestation is negligible when there has been no instrumentation to evacuate the products of conception, and anti-D Ig is not required in these circumstances.

Evidence level 3/4

6.1.2 Threatened miscarriage

Anti-D Ig should be given to all non-sensitised RhD-negative women with a threatened miscarriage after 12^{+0} weeks of gestation. In women in whom bleeding continues intermittently after 12^{+0} weeks of gestation, anti-D Ig should be given at 6-weekly intervals. D

Anti-D Ig should be considered in non-sensitised RhD-negative women if there is heavy or repeated bleeding or associated abdominal pain as gestation approaches 12^{+0} weeks. D

Evidence that women are sensitised after uterine bleeding in the first 12 weeks of pregnancy where the fetus is viable and the pregnancy continues is scant,[18] although there are very rare examples.[19] Against this background, routine administration of anti-D Ig cannot be recommended. However, it may be prudent to reconsider if there is heavy or repeated bleeding or associated abdominal pain, particularly if these events occur as gestation approaches 12^{+0} weeks. The period of gestation should be confirmed by ultrasound.

Evidence level 3

6.1.3 Ectopic pregnancy

Anti-D Ig should be given to all non-sensitised RhD-negative women who have an ectopic pregnancy, regardless of management. D

Alloimmunisation has been reported following ectopic pregnancy and 25% of cases of ruptured tubal ectopic pregnancy are associated with a significant number of fetal cells in the maternal circulation.[20] There is a paucity of evidence regarding the risk of alloimmunisation associated with medical and conser-

vative management of ectopic pregnancy. However, given the potential for sensitisation, it is reasonable to offer anti-D Ig.

6.1.4 Therapeutic termination of pregnancy

Anti-D Ig should be given to all non-sensitised RhD-negative women having a therapeutic termination of pregnancy, whether by surgical or medical methods, regardless of gestational age. D

7. Prophylaxis following sensitising events before delivery

7.1 Which antenatal sensitising events require anti-D Ig prophylaxis?

A minimum dose of 250 iu is recommended for prophylaxis following sensitising events up to 19^{+6} weeks of gestation. For all events at or after 20^{+0} weeks of gestation, a minimum dose of 500 iu anti-D Ig should be given and a test to identify FMH greater than 4 ml red cells performed; additional anti-D Ig should be given as required. D Evidence level 4

In the event of recurrent vaginal bleeding after 20^{+0} weeks of gestation, anti-D Ig should be given at a minimum of 6-weekly intervals. D Evidence level 4

Anti-D Ig should be given to all non-sensitised RhD-negative women after the following potentially sensitising events during pregnancy; this should be in addition to any already received:

- invasive prenatal diagnosis (amniocentesis, chorion villus sampling, cordocentesis, intrauterine transfusion)
- other intrauterine procedures (e.g. insertion of shunts, embryo reduction, laser)
- antepartum haemorrhage
- external cephalic version of the fetus (including attempted)
- any abdominal trauma (direct/indirect, sharp/blunt, open/closed)
- fetal death.

If there is concern about the frequency of recurrent bleeding, estimation of FMH using a Kleihauer test can be performed at 2-weekly intervals; if positive, an additional dose of anti-D Ig can be administered (500 IU or greater, depending on the size of the FMH).[21] This dose is given irrespective of the presence or absence of passive anti-D.

8. Routine antenatal prophylaxis

8.1 How should an RAADP programme be put into clinical practice?

RAADP should be offered to all non-sensitised RhD-negative women. B Evidence level 2++

RAADP is not required in women who are RhD sensitised. ✓

RAADP is a completely separate entity from the anti-D Ig required for potentially sensitising events. ✓

There is no evidence that the efficacy of the single-dose and two-dose regimens differs, and the chosen regimen will depend on local organisational factors. ✓

Women who are eligible for RAADP should receive written information before making an informed decision about opting for treatment. ✓

Consent should be obtained and recorded in the case notes.

✓

The routine 28-week antibody screening sample must be taken before administration of the first dose of anti-D. This meets the British Committee for Standards in Haematology requirement for a second antibody screen during pregnancy.[19]

C Evidence level 2+

Maternal alloimmunisation continues to occur despite administration of anti-D for recognised sensitising events. In some cases this is because of failure to comply with anti-D prophylaxis guidelines. However, in a significant proportion of cases (55–80%) there is no recognised sensitising event and sensitisation is 'silent' secondary to occult FMH.[5,7] This occurs with increasing frequency as gestation advances, with quoted rates for FMH in the third trimester of 45.4%.[22] Fewer than 10% of cases of silent FMH occur before 28 weeks of gestation.The rationale for RAADP is to protect against these unpredictable sensitisations and thus prevent complications and potential morbidity in subsequent pregnancies. In the absence of RAADP, approximately 1% of RhD-negative women who deliver an RhD-positive baby will become sensitised.[10] There are two regimens for providing RAADP: two doses of 500 iu anti-D Ig at 28 and 34 weeks of gestation, or a single dose of 1500 iu at 28 weeks of gestation.

RAADP does reduce the incidence of rhesus alloimmunisation in previously non-sensitised RhD-negative women who deliver an RhD-positive baby.The trials establishing this effect, which are of mixed quality, are described in detail in the NICE guideline and Health Technology Assessment.[2,3] Meta-analysis of the data from the two most clinically relevant trials, both community-based UK studies,[23,24] indicates that the rate of sensitisation in a subsequent pregnancy is reduced from 0.95% to 0.35%.This represents an odds ratio of 0.37 (95% CI 0.21–0.65). On the basis of this absolute reduction in risk of 0.6%, the number of Rh-negative women needed to treat to prevent one case of sensitisation is 166.The overall number needed to treat is 278 as only 60% of RhD-negative women will be carrying an RhD-positive baby.The reduction in sensitisation rates may not be attributable solely to RAADP. There is evidence that the introduction of an RAADP programme increases awareness of the need to administer anti-D Ig following vaginal bleeding and antepartum haemorrhage.[24]

Evidence level 2++

There is evidence that RAADP given in a first pregnancy continues to confer benefit in subsequent pregnancies, although the mechanism for this remains unexplained.[25] A policy of restricted prophylaxis in which only non-sensitised RhD-negative women with no living children were given RAADP confirmed this finding of continuing long-term protection against sensitisation in subsequent pregnancies.[26]

There are no studies comparing the efficacy of the single-dose and two-dose regimen of RAADP.The two-dose regimen results in a slightly higher residual anti-D level at term.A small proportion of women will have undetectable levels of anti-D 12 weeks after a single injection of 1500 iu of anti-D Ig.[27] Therefore, if anti-D Ig is given at 28 weeks of gestation, there is a risk that some women will be unprotected if their pregnancy progresses beyond 40 weeks of gestation. However, if anti-D Ig is administered later than 28 weeks of gestation, the proportion of occult FMH that will be not be covered will increase.There have been concerns that compliance with the two-dose regimen might be poorer than with a single-dose regimen.[28] However, there is evidence that women refusing anti-D Ig do so at the first dose, hence a single-dose regimen is unlikely to have a significant impact on compliance rates.[29]

RAADP and anti-D Ig for sensitising events should be viewed as completely separate entities. RAADP is not an alternative to anti-D Ig for sensitising events and vice versa. RAADP should be given irrespective of whether anti-D Ig has been given at an earlier gestation, for example for prenatal diagnosis or vaginal bleeding. Similarly, sensitising events that occur after administration of RAADP should be covered with an additional dose of anti-D Ig (500 iu, unless Kleihauer testing indicates that a larger dose is required).

As a result of RAADP and prophylactic anti-D Ig for sensitising events, more maternal samples will demonstrate low levels of anti-D on testing. The difficulty is knowing whether this represents passive (prophylactic) or immune anti-D. Passive anti-D can be detected for up to 8 weeks following administration (and in some cases for longer with more sensitive tests), and levels are generally ≤1 iu/ml. Accurate documentation of anti-D Ig administration will help to differentiate between passive and immune anti-D in many cases. Anti-D quantification can be requested in cases where there is significant doubt about the nature of the anti-D. Anti-D prophylaxis should continue unless or until it becomes established that the anti-D is immune.[30] In that event, the woman will be sensitised and further anti-D administration in the current or future pregnancies will not be required.

8.2 What are the maternal and fetal effects of RAADP?

There is no evidence to suggest that RAADP is associated with adverse events that are of consequence for the mother or baby, other than the possibility of blood-borne infection, and procedures are in place to minimise these risks. B

No serious adverse events were reported in the clinical studies reviewed in the 2009 Health Technology Assessment. Information from manufacturers indicates a very low rate of adverse event reporting (<1/85 000 doses) with only a minority of these classified as serious and possibly related to treatment. There is the potential that circulating passive anti-D could augment the primary immune response to rhesus-positive cells following FMH. This has not been observed in clinical trials.[31] Passive anti-D can interact with fetal cells to cause a weak positive direct antiglobulin test. However, there is no evidence that transfer of passive anti-D to the fetus results in haemolysis sufficient to cause fetal anaemia.[31] Evidence level 1+

8.3 How should women who decline RAADP be managed?

Women should be given the opportunity to discuss the benefits and risks so that they can make an informed choice about RAADP. ✓

The availability of a standardised information leaflet about RAADP is recommended by NICE. ✓

If RAADP is declined, this should be documented in the case notes along with the reasons for the decision. ✓

In the event that RAADP is declined antibody screening should be performed at booking and at 28 weeks of gestation to identify cases where sensitisation has occurred. Sensitisation occurring in the third trimester is unlikely to cause significant fetal problems in that pregnancy. C Evidence level 2+

Some women will decline RAADP, and certain subgroups can be identified:

- women who object on religious grounds
- women who will be sterilised after the birth
- women who are certain they will have no more children
- women who are in a stable relationship with the genetic father of their children and the father is known or found to be RhD-negative.

Although it is desirable to avoid unnecessary RAADP, there are potential problems with the latter two groups: women may change their minds about a further pregnancy, and there are known complexities associated with paternal testing with potential for misidentification of the father. The study by MacKenzie et al.[28] found that the percentage of women refusing at least Evidence level 2+

one RAADP injection increased from 0.8% in the period 1992–1996 to 3.5% in 1997–2003. Some of these refusals were at a time when there were public concerns about infection with blood products. However, although a subsequent study demonstrated a higher refusal rate (22/207 eligible women), only one refusal was related to concerns about infection.[29] Women should be given adequate information with which to make an informed choice about accepting or declining anti-D Ig. If a woman declines anti-D Ig, this decision should be acknowledged and the reasons for the decision documented in the case notes.

Evidence level 2+

9. Postnatal prophylaxis

9.1 Who should receive postnatal anti-D Ig prophylaxis?

At least 500 IU of anti-D Ig must be given to every non-sensitised RhD-negative woman within 72 hours following the delivery of an RhD-positive infant. A/B

A test to detect FMH greater than 4 ml must also be undertaken so that additional anti-D Ig can be given as appropriate. C/D

If the pregnancy is non-viable and no sample can be obtained from the baby, anti-D Ig should be administered to a non-sensitised RhD-negative woman. D Evidence level 4

At least 500 iu of anti-D Ig must be given to every non-sensitised RhD-negative woman within 72 hours following the delivery of an RhD-positive infant. This includes women with alloantibodies other than anti-D. There is no universal policy regarding the postnatal dose, which varies in different countries; 1500 iu (300 micrograms) is the standard dose in the USA, 500–600 iu (100–120 micrograms) in Canada and 1000–1250 iu (200–250 micrograms) in many European countries except the UK, Ireland and France. The Medical Research Council dosage trial[32] showed that 500 iu (100 micrograms) of anti-D Ig given intramuscularly, which is capable of suppressing immunisation by 4 ml of RhD-positive red cells, was as effective as both 1500 iu and 1000 iu when used in conjunction with testing to assess the size of FMH.

Evidence level 1+

Some women who have received anti-D Ig during pregnancy may have detectable anti-D in their blood at delivery. Because it may be difficult or impossible to distinguish between such passive anti-D Ig and weak anti-D resulting from early immunisation, anti-D Ig should be given to any eligible woman with weak anti-D antibody at delivery unless it has been clearly confirmed that she is already sensitised.

10. What is the role of non-invasive assessment of fetal blood type?

At present, it is recommended that all RhD-negative women are offered RAADP. The disadvantage of this policy is that approximately 40% of RhD-negative women receive unnecessary antenatal anti-D Ig while carrying an RhD-negative child. This equates to approximately 40 000 women in the UK currently receiving unnecessary prophylaxis.[10] The breakthrough in fetal blood group genotyping has come with the development of cell-free fetal DNA (cffDNA) from maternal plasma. Numerous studies have now been published regarding the accuracy of determination of fetal RhD status from cffDNA. A meta-analysis of 37 studies published between 1993 and 2005 found that using cffDNA from maternal plasma produced an overall diagnostic accuracy of 96.5%.[33] Further improvement in accuracy has continued in more recent studies and now, in addition to ascertaining RhD status, other rarer antigens can be identified. These include K (Kell), Rh C, c and E.[34] The current status of this technology within UK clinical practice is mainly confined to women at high risk of haemolytic disease where there is a partner with a heterozygous genotype. In this situation, knowledge of the fetal blood type would affect the management of the pregnancy. The Reference Laboratory in Bristol has offered this service since 2001. A full description of the issues concerning non-invasive assessment of fetal blood type can be found in the report by the Public Health Genetics Foundation

on cffDNA for non-invasive prenatal diagnosis.[35] It is anticipated that, following publication of further funded studies in this area, a technology assessment will be carried out to inform NICE and the National Screening Committee.

11. Transfusion of RhD-positive blood components

11.1 How should inadvertent transfusion of RhD-positive platelets be managed?

In the event that RhD-positive platelets are transfused, prophylaxis against Rh alloimmunisation should be given. D

It should usually be possible to provide RhD-negative platelets for women of childbearing age who need a platelet transfusion. Occasionally, if an appropriate product is not available, it may be necessary to use RhD-positive platelets. In these circumstances, prophylaxis against possible Rh alloimmunisation by red cells contaminating the platelet product should be given.[36] Evidence level 4

Each unit of platelets prepared according to the UK guidelines from one whole blood donation contains fewer than 1 x 10^9 (< 0.1 ml red cells). 250 iu (50 micrograms) anti-D Ig should be given following every three adult doses (i.e. derived from up to 18 routine donations) of platelets. Women who have marked thrombocytopenia should be given the anti-D Ig subcutaneously to avoid the possibility of a haematoma following intramuscular injection.

11.2 How should inadvertent transfusion of RhD-positive blood be managed?

Anti-D Ig should be given to RhD-negative women of reproductive capacity who inadvertently receive a transfusion of RhD-positive blood. D

The dose should be calculated on the basis that 500 iu of anti-D Ig will suppress immunisation by 4 ml of RhD-positive red blood cells. D

Exchange transfusion may be necessary for large volumes of transfused blood. D

When less than 15 ml of RhD-positive blood hase been transfused to an RhD-negative woman capable of childbearing, the appropriate dose of anti-D Ig should be given. When more than 15 ml has been transfused, it is preferable to use the larger anti-D Ig intramuscular preparation (2500 iu or 5000 iu).

When more than two units of RhD-positive blood have been transfused, consideration should be given to undertaking an exchange transfusion to reduce the load of RhD-positive red blood cells in the circulation and the dose of anti-D Ig required to suppress immunisation. In this situation, the woman should be counselled regarding the implications of both non-intervention (for future pregnancies) and of treatment, including any hazards from receiving donated blood, the exchange procedure itself and of larger doses of anti-D Ig including intravenous anti-D Ig.

Immediate exchange transfusion will reduce the load of RhD-positive red cells (a single-blood-volume exchange will achieve a 65–70% reduction in RhD-positive cells, and a two-volume exchange 85–90%). Following exchange transfusion, the residual volume of RhD-positive red cells should be estimated using flow cytometry or rosetting. Intravenous anti-D Ig is the preparation of choice, achieving adequate plasma levels immediately and being twice as effective microgram for microgram as intramuscular anti-D Ig at clearing red cells. The dose to be administered should assume that 600 iu of intravenous anti-D Ig will suppress immunisation by 10 ml of fetal red cells. Intravenous anti-D Ig is available for use in the UK on a named patient basis only as WinRho SDF or Rhophylac. Intramuscular anti-D Ig must not be given intravenously. An appropriate combined dose of intravenous and intramuscular anti-D Ig should be determined in discussion with a specialist in transfusion medicine. Follow-up tests for RhD-positive red

cells should be undertaken every 48 hours and further anti-D Ig given until all RhD-positive red cells have been cleared from the circulation. Free anti-D in the woman's serum does not necessarily reflect adequate prophylaxis and anti-D Ig treatment should be continued until RhD-positive red cells are no longer detectable.

Passive anti-D Ig given in large doses may be detectable for up to 6 months or more and tests for immune anti-D may not be conclusive for 9–12 months.

12. Documentation and audit of anti-D administration

European Union guidance recommends that the necessary records are kept to ensure traceability of all blood products; this includes anti-D Ig.[37] The laboratory and maternity services should therefore keep complete records of issues and administration of anti-D Ig so that traceability of anti-D Ig is possible. It is recognised that local arrangements may vary as to how this is achieved.[19]

13. Suggested audit topics

- The proportion of non-sensitised RhD-negative women receiving anti-D Ig after a sensitising event or delivery of an RhD-positive baby.
- Proportion of FMH tests carried out for sensitising events at or beyond 20 weeks of gestation and at delivery of an RhD-positive baby.
- The uptake of RAADP by non-sensitised RhD-negative women.
- Availability of an information leaflet for RAADP.
- Documentation of an informed consent process for RAADP.
- The proportion of women receiving anti-D Ig at 28 and 34 weeks of gestation (two-dose regimen) and at 28 weeks of gestation (single-dose regimen).
- The proportion of women receiving anti-D Ig within 1 week of the recommended gestation for either regimen.
- Documentation of the reasons given by women who decline RAADP.
- Documentation to ensure traceability of anti-D Ig from source to recipient.

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Appendix

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

This guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by:

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

The guideline review process will commence in 2014 unless evidence requires earlier review.

