Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Guideline No. 22

(Reviewed May 2002)

USE OF ANTI-D IMMUNOGLOBULIN FOR RHESUS PROPHYLAXIS

This guideline should be read in conjunction with the National Institute for Clinical Excellence's Technology Appraisal Guidance No. 41, *Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women*, May 2002.

1. Introduction

The development of anti-D antibodies generally results from fetomaternal haemorrhages (FMH) occurring in RhD negative women who carry 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]

Guidelines on Rh immunoprophylaxis were updated in 1976,[2] 1981[3] and 1991.[4] However RhD alloimmunisation continues to occur. There is clear evidence that the 1991 guidelines are not being fully applied.[5,6] 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 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.[7]

The current recommendations are taken directly from the updated guidelines drawn up by a joint working group of the British Blood Transfusion Society and the Royal College of Obstetricians and Gynaecologists.[8]

2. Test for the size of fetomaternal haemorrhage

Studies have shown that 99.2–99.3% of women have a FMH less than 4 ml at delivery. Up to 50% of larger FMHs occur after normal deliveries.[9] However, the following clinical circumstances are more likely to be associated with large FMH:

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

Tests to estimate the size of the FMH are recommended in many countries including the UK, the USA, Canada, France and Ireland, although not in most European countries. While the Kleihauer acid elution test which detects fetal haemoglobin (HbF) is the test usually undertaken in the UK and Canada, tests which specifically identify RhD positive red cells are used in the USA.

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.[10] Unfortunately, this policy does not take account of the fact that up to 0.3% of women have a 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 will receive less protection than they do now. The recommended policy in the UK is to obtain an anticoagulated blood sample as soon as possible (within two hours) after delivery and to undertake a Kleihauer screening test to identify women with a large FMH who need additional anti-D Ig **(Grade B recommendation)**.

Flow cytometry offers an alternative technique for quantifying the size of FMH.[11] It 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 patients with high HbF levels. Not all hospitals will have ready access to a flow cytometer though 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[1] is a relatively simple serological method which offers another alternative for quantifying FMH of RhD positive red cells greater than 4ml.

3. Anti-D Ig preparations available in the UK

Until 1994, only anti-D Ig prepared from immune plasma donated by unpaid UK volunteer donors, either by the Bio Products Laboratory (BPL) or by the Scottish Protein Fractionation Centre (PFC) was available in the UK. Recently, imported anti-D Ig has been licensed in the UK. It should be noted that imported products may be prepared from plasma collected from paid donors within and outside the EC. The currently available preparations are:

BPL (intramuscular)
(i) 250 iu (50 micrograms)
(ii) 500 iu (100 micrograms)
(iii) 2500 iu (500 micrograms)

PFC (intramuscular)
(i) 250 iu (50 micrograms)
(ii) 500 iu (100 micrograms)
(iii) 5000 iu (1000 micrograms)

IMPORTED
(i) Intramuscular 1250 iu (250 micrograms) “Partobulin” from IMMUNO (licensed in the UK).

(ii) Intravenous 600 iu (120 micrograms) or 1500 iu (300 micrograms) from WINRHO (not licensed in the UK).

In view of the theoretical risk of nvCJD posed by UK plasma all anti-D produced by BPL and PFC is now manufactured from US plasma.

4. Administration

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.

For successful immunoprophylaxis, anti-D Ig should be given as soon as possible after the 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 9–10 days may provide some protection **(Grade B recommendation)**. Women who are already sensitised should not be given anti-D Ig.

Women who have a weak expression of the RhD blood group (D^u) do not form anti-D and do not therefore 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.

5. Prophylaxis following abortion

Some RhD negative women require anti-D Ig following abortion; 250 iu before 20 weeks of gestation and 500 iu thereafter. A test for the size of FMH should be performed when anti-D Ig is given after 20 weeks.

5.1 **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 **(Grade B recommendation)**.

5.2 **Ectopic pregnancy:** Anti-D Ig should be given to all non-sensitised RhD negative women who have an ectopic pregnancy **(Grade B recommendation)**.

5.3 **Spontaneous miscarriage:** Anti-D Ig should be given to all non-sensitised RhD negative women who have a spontaneous complete or incomplete abortion after 12 weeks of pregnancy **(Grade B recommendation)**. Published data on which to base recommendations in earlier miscarriages are scant. There is evidence that significant FMH only occurs after curettage to remove products of conception but does not occur after complete spontaneous miscarriages.[12,13] Anti-D Ig should therefore be given when there has been an intervention to evacuate the uterus. On the other hand, the risk of immunisation by spontaneous miscarriage before 12 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 **(Grade C recommendation)**.

5.4 **Threatened miscarriage:** Anti-D Ig should be given to all non-sensitised RhD negative women with a threatened miscarriage after 12 weeks of pregnancy. Where bleeding continues intermittently after 12 weeks' gestation, anti-D Ig should be given at six-weekly intervals **(Grade C recommendation)**. 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[14] though there are very rare examples.[15] Against this background, routine administration of anti-D Ig cannot be recommended. However it may be prudent to administer anti-D Ig where

bleeding is heavy or repeated or where there is associated abdominal pain particularly if these events occur as gestation approaches 12 weeks **(Grade C recommendation)**. The period of gestation should be confirmed by ultrasound.

6. Prophylaxis following sensitising events before delivery

Anti-D Ig should be given to all non-sensitised RhD negative women after the following potentially sensitising events during pregnancy:

- invasive prenatal diagnosis (amniocentesis, chorion villus sampling, fetal blood sampling)
- other intrauterine procedures (e.g. insertion of shunts, embryo reduction)
- antepartum haemorrhage
- external cephalic version of the fetus
- closed abdominal injury
- intrauterine death.

A dose of 250 iu is recommended for prophylaxis following sensitising events up to 20 weeks of pregnancy. For all events after 20 weeks, at least 500 iu anti-D Ig should be given followed by a test to identify FMH greater than 4ml red cells; additional anti-D Ig should be given as required **(Grade B recommendation)**.

7. Postnatal 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 a RhD positive infant **(Grade B recommendation)**. 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 MRC dosage trial[16] showed that 500 iu (100 micrograms) of anti-D Ig given intramuscularly, which is capable of suppressing immunisation by 4–5 ml of RhD positive red cells, was as effective as both 1500 iu and 1000 iu.

A test to detect FMH greater than 4 ml must also be undertaken, so that additional anti-D Ig can be given as appropriate **(Grade B recommendation)**.

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 **(Grade B recommendation)**.

8. Routine antenatal prophylaxis

Click here for NICE's guidance on the use of routine antenatal prophylaxis.
(http://www.nice.org.uk/cat.asp?c=31679)

9. Transfusion of RhD positive blood components

9.1 **RhD positive platelet transfusions:** 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[17] **(Grade B recommendation)**.

Each unit of platelets prepared according to the UK Guidelines from one whole blood donation contains less than 1 X 109 (< 0.1 ml rbc). 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. Patients who have marked thrombocytopenia should be given the anti-D Ig subcutaneously to avoid the possibility of a haematoma following intramuscular injection.

9.2 **Inadvertent transfusion of RhD positive blood:** When less than 15 ml of RhD positive blood has been transfused to a RhD negative woman capable of childbearing, the appropriate dose of anti-D Ig should be given (Grade B recommendation). When more than 15 ml has been transfused, it is preferable to use the larger anti-D Ig IM preparation (2500 iu or 5000 iu). 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 (rbc) **(Grade B recommendation)**.

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 patient 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 IV anti-D **(Grade C recommendation)**.

Immediate exchange transfusion will reduce the load of RhD positive rbc (a one-blood-volume exchange will achieve a 65–70% reduction in RhD positive cells; 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 micrograms as intramuscular anti-D at clearing rbc. The dose to be administered should assume that 500 iu of anti-D Ig iv will suppress immunisation by 8–10 ml of fetal rbc. Intravenous anti-D Ig is available for use in the UK on a named-patient basis only from WINRHO (Canada). 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 rbc 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 patient's serum does not necessarily reflect adequate prophylaxis and anti-D Ig treatment should be continued until RhD positive rbc are no longer detectable.

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

10. Conclusion and summary of recommendation

RhD immunisation continues to occur. In some cases this results from failure to adhere to previously published guidelines on RhD prophylaxis. However the most important cause of anti-D is now

immunisation during pregnancy where there has been no overt sensitising event. This problem is not covered by previous guidelines.

The key recommendations of the current guidelines are as follows:

- Following delivery, irrespective of the dose of anti-D Ig routinely administered, postnatal prophylaxis must include a screening test to identify women with a large FMH who need additional immunoglobulin **(Grade B recommendation)**.
- Anti-D Ig should be given after sensitising events before delivery and after abortion **(Grade B recommendation)**.
- Anti-D Ig is no longer necessary in women with threatened miscarriage with a viable fetus and cessation of bleeding before 12 weeks of gestation (Grade C recommendation).
- At least 500 iu of anti-D Ig should be given to non-sensitised RhD negative women at 28 weeks and 34 weeks of pregnancy according to NICE guidance **(Grade A recommendation)**.

It is important that women have all the necessary information to enable them to make an informed choice about Rh prophylaxis. Information sources must indicate that anti-D Ig is a blood product. There is now an urgent need to address the implementation and monitoring of the new guidelines.

References

1. Mollinson PL, Engelfriet CP, Contreras M. Haemolytic disease of the fetus and newborn. In: Blood Transfusion in Clinical Medicine. 10th Edition. Blackwell Science 1997; 414.

2. Standing Medical Advisory Committee. *Haemolytic Disease of the Newborn*. London: Department of Health and Social Security, 1976.

3. Standing Medical Advisory Committee. *SMAC memorandum on haemolytic disease of the newborn - 1976: - addendum -1981*. London: Department of Health and Social Security, 1982.

4. Recommendations for the use of anti-D immunoglobulin. Prescribers' Journal 1991; **31**:137-45.

5. Hughes RG, Craig JI, Murphy WG, Greer IA. Causes and clinical consequences of Rhesus (D) haemolytic disease of the newborn: a study of a Scottish population, 1985-1990. Br J Obstet Gynaecol 1994; **101**:297-300.

6. McSweeney E, Kirkham J, Vinall P, Flanagan P. An audit of anti-D sensitisation in Yorkshire. Br J Obstet Gynaecol 1998; **105**:1091-4.

7. Robson SC, Lee D, Urbaniak S. Anti-D immunoglobulin in RhD prophylaxis. Br J Obstet Gynaecol 1998; 129-134.

8. Joint Working Group of the British Blood Transfusion Society and the RCOG. Recommendations for the use of anti-D immunoglobulin for Rh prophylaxis. Transfusion Medicine 1999, **9**:93-7.

9. Ness PM, Baldwin ML, Niebyl JR. Clinical high-risk designation does not predict excess fetal-maternal haemorrhage. Am J Obstet Gynecol 1987; **156**:154-8.

10. Commission of the European Communities, Brussels. Committee for Proprietary Medicine Products. Notes for guidance: core summary of product characteristics for human anti-D immunoglobulin IM. 1994: III/34463/92-EN.

11. Johnson PR, Tait RC, Austen EB, Shwe KH, Lee, D. Flow cytometry in diagnosis and management of large feto-maternal haemorrhage. J Clin Path 1995; **48**:1005-8.

12. Jorgensen J. *Feto-maternal bleeding*. MD Thesis, University of Copenhagen, 1975.

13. Matthews CD, Matthews AE. Transplacental haemorrhages in spontaneous and induced abortion. Lancet 1969; **I**:694-5.

14. Ghosh, Murphy WG. Implementation of the rhesus prevention programme: a prospective study. Scott Med J 1994; **39**:147-9.

15. Whitfield CR. Personal communication, 1997.

16. Controlled trial of various anti-D dosages in suppression of Rh sensitization following pregnancy. Report to the Medical Research Council of a Working Party on the use of anti-D - immunoglobulin for the prevention of isoimmunization of Rh-negative women during pregnancy. BMJ 1974; **2**:75-80.

17. Murphy MF, Lee D. Dose of anti-D immunoglobulin for the prevention of RhD immunisation after RhD-incompatible platelet transfusions (letter). Vox Sang 1993; **65**:73-4.

Individual recommendations have been graded according to the level of evidence on which they are based using the scheme endorsed by the NHS Executive: Grade A: randomised controlled trials Grade B: other robust experimental or observational studies Grade C: more limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities

This guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by Professor S C Robson MRCOG, Newcastle-upon-Tynes.

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

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Unless otherwise indicated