

Frequently asked Questions about the use of Rh (D) Immunoglobulin

Abbreviations used in this section:

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| FMH | Fetomaternal Haemorrhage |
| HDN | Haemolytic Disease of the Newborn |
| IU | International Units |
| RANZCOG | Royal Australian and New Zealand College of Obstetricians and Gynaecologists |
| ARCBS | Australian Red Cross Blood Service |

NHMRC Report (1999): National Health and Medical Research Council (NHMRC) *Guidelines on the prophylactic use of Rh (D) immunoglobulin (Anti-D) in obstetrics 1999*

NHMRC Report (2003): National Health and Medical Research Council (NHMRC) *Guidelines on the prophylactic use of Rh D immunoglobulin (Anti-D) in obstetrics 2003*

Clinical Questions & Answers

Introduction

The following answers have been prepared and endorsed by RANZCOG. The information provided is consistent with the recommendations of the NHMRC reports (1999 and 2003), which are based on an extensive literature review.

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QUESTIONS & ANSWERS

1. Administration of Rh (D) immunoglobulin for sensitising events

1.1 *During what timeframe should Rh (D) immunoglobulin be administered after a potentially sensitising event for successful immunoprophylaxis?*

For successful immunoprophylaxis, Rh (D) immunoglobulin should be administered as soon as possible after the sensitising event, but always within 72 hours. Blood should be taken from the mother before administration of the Rh (D) immunoglobulin to assess the magnitude of fetomaternal haemorrhage FMH. Where FMH quantitation shows that FMH greater than that covered by the dose already administered has occurred, administration of an additional dose(s) sufficient to provide immunoprophylaxis must be administered and preferably within 72 hours. Assessment of FMH by Kleihauer testing is generally not indicated in the first or second trimesters.

If Rh (D) immunoglobulin has not been offered within 72 hours, a dose offered within up to 9-10 days may provide protection. During the informed consent process the patient should be advised of the potential consequences of the delay in the administration of Rh (D) immunoglobulin and consideration be given to insurer notification.

1.2 *What are the current recommendations for the administration of Rh (D) immunoglobulin?*

These are summarised in the table below.

| Rh (D) immunoglobulin dosage recommendations for Rh (D) negative women | Dose |
|--|------------------------|
| <i>Obstetric conditions</i> | |
| Sensitising events in the first trimester (up to and including 12 weeks gestation) for every Rh (D) negative woman with no preformed anti-D antibodies. Including: <ul style="list-style-type: none">• miscarriage;• termination of pregnancy;• ectopic pregnancy; and• chorionic villus sampling. | 250 IU (50 µg) |
| Sensitising events beyond the first trimester for every Rh (D) negative woman with no preformed anti-D antibodies. Including: | 625 IU (125 µg) |

- chorionic villus sampling, amniocentesis, cordocentesis and fetoscopy;
- abdominal trauma considered sufficient to cause FMH;
- each occasion of revealed or concealed antepartum haemorrhage (where the patient suffers unexplained uterine pain the possibility of concealed antepartum haemorrhage should be considered, with a view to immunoprophylaxis);
- external cephalic version (performed or attempted); and
- miscarriage or termination of pregnancy.

Pregnancy

Antenatal prophylaxis (at 28 and 34 weeks) for all Rh (D) negative women (Primigravid and Multigravid)

625 IU (125 µg)

Postpartum

625 IU (125 µg)

For every Rh (D) negative woman following delivery of an Rh D positive baby. Rh (D) immunoglobulin should not be given to women with preformed anti-D antibodies, except where the preformed anti-D is due to the antenatal administration of Rh (D) immunoglobulin. If it is unclear whether the anti-D detected in the mother's blood is passive or preformed, the treating clinician should be consulted. If there is continuing doubt, Rh D immunoglobulin should be administered.

The magnitude of the FMH should be assessed by a method capable of quantifying a haemorrhage of ≥ 6 ml of fetal red cells (12 ml of whole blood). Further doses should be administered sufficient to prevent maternal immunisation.

1.3 What is the earliest time frame that an Rh (D) negative woman should receive Rh (D) immunoglobulin for a potentially sensitising event?

The Rh (D) antigen has been identified on fetal erythrocytes as early as 38 days gestation, but there is doubt concerning the risk of sensitisation associated with bleeding before 12 weeks in an ongoing pregnancy or spontaneous abortion before 12 weeks. The available evidence indicates that FMH can occur after six weeks gestation and that sensitisation has been reported as early as 6 weeks gestation.

On the basis of this evidence, the NHMRC Report (2003) recommends that Rh (D) immunoglobulin be given following therapeutic abortion (both medical or surgical), following curettage to remove products of conception (including a blighted ovum), and where bleeding occurs in an ongoing pregnancy beyond the first trimester. There is no evidence available to determine the minimum time in pregnancy

beyond which Rh (D) should be given but RANZCOG recommends that 6 weeks is a reasonable minimum period of gestation.

1.4 *Should Rh (D) immunoglobulin be given for a first trimester spontaneous miscarriage, without a curette?*

The NHMRC Report (2003) states that there is doubt concerning the risk of sensitisation associated with bleeding in a spontaneous abortion before 12 weeks. This means that it is unclear whether or not there is a risk of sensitisation before 12 weeks.

The NHMRC report (2003) recommends that a dose of 250 IU Rh (D) immunoglobulin should be offered to every Rh (D) negative woman with no preformed anti-D antibodies to ensure adequate protection against immunisation for miscarriage (up to and including 12 weeks' gestation).

The NHMRC Report (2003) strongly recommends that women undergoing termination of pregnancy be tested to determine their Rh (D) type, to avoid unnecessary use of Rh (D) immunoglobulin.

Note: the UK RCOG do not recommend routine administration of anti D for threatened miscarriage with a viable fetus <12 weeks, nor for spontaneous miscarriage without instrumentation to evacuate the products of conception.

1.5 *Should Rh (D) immunoglobulin be given for a missed abortion, having a curette?*

The NHMRC Report (2003) recommends that Rh (D) immunoglobulin be given following therapeutic abortion and following curettage to remove products of conception. This should include curettage for a missed abortion.

The NHMRC Report (2003) strongly recommends that women undergoing termination of pregnancy be tested to determine their Rh (D) type, to avoid unnecessary use of Rh (D) immunoglobulin.

1.6 *Should Rh (D) immunoglobulin be given for first trimester bleeds that do not result in miscarriage?*

The NHMRC Report (2003) states that there is insufficient evidence to support the use of Rh (D) immunoglobulin in bleeding prior to 12 weeks' gestation in an ongoing pregnancy, although if the pregnancy then requires curettage Rh (D) immunoglobulin should be given. If the bleeding is particularly heavy or associated with a visible subchorionic haemorrhage these patients should be considered at higher risk of sensitisation and Rh (D) given.

1.7 *If a sensitising event occurs shortly after a prophylactic dose of Rh (D) immunoglobulin has been given, should a further dose of Rh (D) immunoglobulin be given?*

The magnitude of the FMH should be quantified and then the appropriate dose of Rh (D) immunoglobulin given.

1.8 *What should be the time frame between doses of Rh (D) immunoglobulin for recurrent bleeds in pregnancy?*

Howard et al (1997) reported that Rh (D) immunoglobulin should be given every six weeks if women continue to bleed, as recommended in the National Blood Transfusion Services Immunoglobulin Working Party guidelines (NBTS Immunoglobulin Working Party 1991). In such situations it would be prudent to measure the size of any FMH.

1.9 *What dose of Rh (D) immunoglobulin is recommended for sensitising events in multiple pregnancy?*

It is recommended that 625 IU Rh (D) immunoglobulin is given for potentially sensitising events during the first trimester for multiple pregnancy. For sensitising events beyond the first trimester it is recommended that the size of the FMH is determined and the appropriate dose of Rh (D) immunoglobulin then given.

2. Postpartum Prophylaxis

2.1 *What percentage of women will develop Rh (D) antibodies if Rh (D) immunoglobulin is given only at delivery?*

The NHMRC Report (1999) states that immunisation occurs during pregnancy in about 1.5 % of Rh (D) negative women carrying an Rh (D) positive infant, where Rh (D) immunoglobulin is only given at delivery.

2.2 *If Rh (D) immunoglobulin is given for a sensitising event, is it still necessary to give Rh (D) immunoglobulin prophylactically postnatally?*

Yes, as you cannot be sure of the amount of passive antibody remaining after the sensitising event.

3. Antenatal Prophylaxis

3.1 *What is the percentage rate of protection if Rh (D) immunoglobulin is also given antenatally?*

The NHMRC Report (1999) states that the immunisation rate can be reduced to 0.2 % or less by the administration of Rh (D) immunoglobulin during pregnancy, at 28 weeks and 34 weeks, as well as after delivery.

3.2 *What dose of Rh (D) immunoglobulin is recommended for antenatal prophylaxis in multiple pregnancy?*

625 IU Rh (D) immunoglobulin should be given for antenatal prophylaxis in multiple pregnancy.

3.3 *If Rh (D) immunoglobulin is given for a sensitising event, is it still necessary to give Rh (D) immunoglobulin prophylactically at 28 and 34 weeks?*

Yes, as you cannot be sure of the amount of passive antibody remaining after the sensitising event. Antenatal prophylaxis doses should be given in addition to doses administered for sensitising events.

3.4 *If a patient fails to receive prophylactic Rh (D) immunoglobulin at 28 weeks, should they receive the dose at 34 weeks?*

The dose should be given as soon as possible after it is recognised that the dose was missed, rather than waiting for the 34 weeks dose. In such a case the second dose should be delayed until 6 weeks after the first dose.

3.5 *What is the effect on the fetus post administration of Rh (D) immunoglobulin?*

Whilst it is reported that 10–15 per cent of the antibody crosses the placenta into the fetal circulation, the NHMRC Report (1999) stated that there is no evidence confirming an adverse effect of passive Rh (D) immunoglobulin on the embryo or fetus. However the studies which looked at safety for the fetus provided data limited to evaluation of the cord haemoglobin, bilirubin and direct Coombs' tests.

The NHMRC Report (2003) conducted a further literature review of the effect of circulating prophylactically administered Rh (D) immunoglobulin in the fetal circulation. One study was found that evaluated signs of haemolysis in babies of Rh (D) negative mothers who underwent prophylaxis with one or two doses of Rh D immunoglobulin during pregnancy. No statistically significant differences were found for any of the haematological variables between the babies of mothers who received one or two doses of Rh (D) immunoglobulin, or between the Rh (D) negative babies and the controls. Therefore the literature search failed to find any new evidence for concern about fetal effects of prophylactic Rh (D) immunoglobulin (either one or two doses).

3.6 *Is there a need to administer a further dose of Rh (D) immunoglobulin if a delivery is delayed beyond 40 weeks' gestation?*

It is a common and widespread practice to offer induction of labour to women who have reached 10 days beyond their due date and now there are very few pregnancies which progress beyond 42 weeks.

In clinical trials, the estimated half-life of Rh (D) Immunoglobulin has been shown to be approximately 4 weeks and it is generally accepted that a dose of 625 IU (125 mcg) of Rh (D) immunoglobulin provides coverage for a period of 6 weeks.

If the half-life is approximately 4 weeks, the difference in antibody level in an uncomplicated pregnancy 6 weeks after the injection as compared to 8 weeks is unlikely to be significant.

It would be expected that any significant FMH event occurring after term would be likely to precipitate labour or lead to medical intervention to deliver the baby and this would then be followed shortly after by the administration of the postnatal dose of Rh (D) immunoglobulin.

Therefore, for an uncomplicated pregnancy that proceeds up to 42 weeks, there is no need to give a further dose of antenatal Rh (D) immunoglobulin.

4. General Questions

4.1 *What is the chance that an Rh (D) negative woman will carry an Rh (D) positive fetus?*

Approximately 17% of Caucasian women and men will be Rh (D) negative.

- This means that approximately 1 in 6 Rh (D) negative women will have a partner who is also Rh (D) negative. If both the mother and the father of the baby are Rh (D) negative, the fetus will always be Rh (D) negative.
- Approximately 5 in 6 Rh (D) negative women will have a partner who is Rh (D) positive. Of these approximately 45% of the fathers will be homozygous for the Rh (D) antigen and 55% will be heterozygous for the Rh (D) antigen.
- If the father of the baby is Rh (D) positive and homozygous for the Rh (D) antigen, the fetus will always be Rh (D) positive.
- If the father of the baby is Rh (D) positive and heterozygous for the Rh (D) antigen, the fetus will have a 50% chance of being Rh (D) negative and a 50% chance of being Rh (D) positive.

These figures are correct as long as paternity can be assumed. In cases of non-paternity, the risk will depend on the rhesus genotype of the biological father. Information from prenatal diagnostic laboratories performing genetic testing has indicated that non-paternity rates may be as high as 20-30%.

4.2 *Where is the best site for administration of the intramuscular injection?*

The deltoid muscle or the anterolateral thigh is the best site.

4.3 *If a patient has an IV line, would you administer Rh (D) immunoglobulin by IV or IM?*

The Australian Rh (D) immunoglobulin product can only safely be given intramuscularly.

In some circumstances, access to an intravenous Rh (D) preparation may be warranted. A quantity of intravenous Rh (D) immunoglobulin has been reserved for this purpose. Contact ARCBS for further information.

4.4 *How common is HDN?*

Until the late 1960s, HDN due to Rh (D) incompatibility was an important cause of fetal and neonatal morbidity and mortality.

Mortality from HDN due to Rh incompatibility is now uncommon.

The rate of severe Rh (D) incompatibility (i.e. where fetal transfusion may be indicated) in Australia & New Zealand is approximately 1 in 5000 pregnancies.

4.5 *What information is available for patients?*

There is a patient information leaflet on Haemolytic Disease of the Newborn, (HDN), available from the NHMRC. A further patient information leaflet is also available from the ARCBS (www.transfusion.com.au) and CSL (www.csl.com.au).

4.6 *What other education /information materials are available for health professionals?*

The following materials are available from ARCBS and CSL Bioplasma:

- You and Your Baby: Important information for Rh (D) negative women: Prevention of Haemolytic Disease of the Newborn (HDN) brochure
- Important information for Rh (D) negative women: Prevention of Haemolytic

Disease of the Newborn (HDN) brochure (For women who experience early fetal loss)

- Approved product information for Rh (D) Immunoglobulin
- Consumer medicine information for Rh (D) Immunoglobulin

To find out how to obtain these materials visit the ARCBS web site: www.transfusion.com.au/RhD or CSL website (www.csl.com.au).

Endorsed by Council November 2005