

EDITORIAL

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Welcome to the first issue of InfoLink for 2004 which is devoted to the topic of Rh D Immunoglobulin. This issue also contains the first InfoLink article by PaLMS new Head of Transfusion Medicine, Dr Amanda Thomson. Prior to taking up her position with PaLMS Dr Thomson was at the Red Cross Blood Transfusion Service whilst simultaneously being a member of the NSW Blood Transfusion Improvement Collaborative. She brings a wealth of experience to the position and we look forward to her ongoing valuable contribution to InfoLink.

Currently there are a number of changes taking place relating to Transfusion Medicine and Rh D Immunoglobulin is one of these. Dr Thomson's article brings all the relevant information together and includes not just the current recommendations for use of Rh D Immunoglobulin but also the more detailed 'Guidelines for the Use of Rh D Immunoglobulin in Rh Negative Pregnant Women'. There have been a number of workshops relating to this topic and Dr Thomson has included a selection of FAQs in her article. Anyone involved in providing obstetric care should find this article invaluable.

PaLMS have a number of useful resources that provide transfusion information for not only health care professionals but also patients. More details can be found on page 4.

If there is a topic you wish covered in future issues or you have any feedback relating to this issue please contact a member of the editorial team whose details appear below.

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Changes in the use of Rh D Immunoglobulin products in Australia: introduction of antenatal prophylaxis

Dr Amanda Thomson, Head of Transfusion Medicine, PaLMS

Background

Rh D immunoglobulin (anti-D) was first used for Rh prophylaxis in 1968 and since then fetal and neonatal deaths due to Rh haemolytic disease of the newborn (HDN) have dramatically fallen. Although immunoprophylaxis is highly successful in preventing Rh D sensitisation, approximately 1- 2% of women at risk still develop anti-D¹. Failures of prophylaxis may occur due to failure to administer anti-D or because of inadequate dosing schedules. However, sensitisations which occurred despite appropriate administration of anti-D were considered to be due to significant fetomaternal haemorrhage (FMH) during the third trimester. Studies subsequently performed showed that the sensitisation rate could be further reduced to less than 0.2% if anti-D was also administered routinely at 28 and 34 weeks gestation¹. In North America and Canada, routine antenatal prophylaxis has been standard practice for more than 15 years and has more recently been adopted by other countries such as the UK and the Netherlands.

Supply of Rh D immunoglobulin in Australia

In 1968, the Australian Red Cross Blood Service (ARCBS) commenced its programme to provide anti-D plasma for production of Rh D immunoglobulin by CSL. Australia was the first country to be self sufficient in the production of Rh D immunoglobulin. Two groups of donors are involved in the programme. The first are the Rh negative donors who are deliberately immunised/boosted to produce high titre anti-D by receiving regular injections of Rh D positive red cells. Plasma is collected from these donors up to every two weeks and many of the donors originally recruited still continue to donate. Many have now given more than 500 donations with the highest more than 800 donations. A second group of donors regularly donate red cells which are extensively tested, or 'accredited', and frozen for 12 months prior to being used as the immunising/boosting cells. The donors in the Rh project have given incredible service without which Australian needs could not have been met.

However, more recently there have been difficulties in maintaining supply. Reasons for this include:

- the progressive retirement of anti-D plasma donors on the grounds of age and declining health
- declining levels of anti-D in the plasmapheresis donors which occurs over time, and the difficulty in increasing antibody levels in these donors
- a fall in the number of women immunised during pregnancy because of the success of the immunization program in recent decades
- fewer men in the community with anti-D: it is now unusual to transfuse Rh D negative individuals with Rh D positive blood, whereas this was relatively common 20 years ago.

The ARCBS has therefore moved to continue to increase the supply of plasma for the manufacture of Rh D immunoglobulin plasma by expanding the anti-D donor recruitment and boosting program.

Hospital transfusion and pathology laboratories can also assist by identifying people with high levels of anti-D antibodies due to previous transfusion or pregnancy and asking whether they are interested in joining the ARCBS anti-D plasmapheresis donor programme.

Guidelines for use of Rh D immunoglobulin

In 1999 the National Health and Medical Research Council (NHMRC) developed Guidelines for the Use of Rh D Immunoglobulin (anti-D) in Obstetrics² in order to guide practice so that appropriate use of Rh D immunoglobulin was ensured. These acknowledged that, in order to minimise the incidence

of Rh D HDN, best practice was to give Rh D negative women anti-D prophylactically (termed routine antenatal prophylaxis) during pregnancy. However, at that time there was not sufficient locally produced Rh D immunoglobulin to support this recommendation and therefore routine antenatal prophylaxis could not be advocated. However, the Guidelines² did recommend the development and implementation of short and long-term strategies to promote the most efficient use of the existing supply and to identify a sustainable means of increasing supply to meet demand.

These developments have subsequently included:

- the introduction of a 250 IU (50ug) dose of Rh D immunoglobulin for sensitising events in the first trimester
- the registration of the Canadian product WinRho SDF™ for use postpartum to supplement local supplies until self sufficiency in plasma supply is achieved
- the provision of Government funding to the ARCBS to allow the collection of additional hyperimmune plasma to CSL Bioplasma for the manufacture of Rh D immunoglobulin.

With implementation of these measures, Rh D immunoglobulin supplies are now adequate and recommendation has been made that staged implementation of routine antenatal prophylaxis can commence. The following table summarises the proposed strategy for implementing full antenatal prophylaxis.

Situation to October 2002	Routine antenatal prophylaxis unable to be recommended
Short-term strategy (began November 2002)	Routine antenatal prophylaxis at 28 and 34 weeks for Rh D negative women during their first pregnancy Supply augmented with imported product
Mid-term strategy (at earliest in second half 2004 but dependent upon plasma supply)	Routine antenatal prophylaxis at 28 and 34 weeks for all Rh D negative women <i>Supply augmented with imported product</i>
Long-term strategy (dependent upon plasma supply)	Routine antenatal prophylaxis at 28 and 34 weeks for all Rh D negative women <i>Australia self-sufficient in Rh D immunoglobulin</i>

In line with the increase in available supplies of Rh D immunoglobulin, the 1999 NHMRC Guidelines have been revised and updated. The updated Guidelines³ are now available on the new National Blood Authority website www.nba.gov.au.

A summary of the updated Guidelines including which Rh D immunoglobulin product and dose is to be used for specific clinical circumstances is provided in the table.

To assist in the implementation of antenatal prophylaxis, ARCBS and CSL Bioplasma have produced a range of educational materials which can be requested by faxing the CSL Immunotherapy Product Manager on 03 93585410.

CURRENT RECOMMENDATIONS FOR USE OF RH D IMMUNOGLOBULIN

	Reason for administration	Dose / manufacturer
<i>ANTENATAL</i>	Potentially sensitising event up to and including 12 weeks gestation	CSL Rh D immunoglobulin 250 IU IMI
	Potentially sensitising event >12 gestation	CSL Rh D immunoglobulin 625 IU IMI
	Antenatal prophylaxis primigravidae (no preformed Anti-D)	CSL Rh D immunoglobulin 625 IU IMI (at 28 and 34 weeks)
	Antenatal prophylaxis -multiparous	Nil
<i>POSTNATAL</i>	RH D positive baby	WinRho 600 IU IMI
	RH D negative baby	Nil

Administration of Rh D immunoglobulin

It is important to obtain the patient’s consent for the administration of Rh D immunoglobulin and to correctly document in each patient’s notes/record when RhD immunoglobulin was administered including:

- date of administration
- dose/route
- manufacturer
- any adverse reactions

If documentation of the antenatal administration of Rh (D) immunoglobulin is omitted, it can compromise the interpretation of subsequent antibody testing results and therefore potentially impact on patient care.

PaLMS Transfusion Medicine Educational Resources

Suitable for Doctors, nurses, scientists and technicians

- ★ **Guide to Blood Transfusion: Information for Health Care Professionals (Booklet)**
- ★ **Right Blood – Right Patient (A4 Full Colour Laminated Poster)**

Suitable for Patients and/or their families

- ★ **Transfusion, important patient information: Your Guide to Blood Transfusion**

For supplies of any of the above contact PaLMS Administration on 9926 8086 or a member of the Editorial Team.

GUIDELINES FOR THE USE OF RH D IMMUNOGLOBULIN IN RH NEGATIVE PREGNANT WOMEN

General:

For successful immunoprophylaxis, Rh D immunoglobulin should be administered as soon as possible after the sensitising event, but always within 72 hours. If Rh D immunoglobulin has not been given within 72 hours a dose given within 9-10 days may offer some protection. Blood should be taken from the mother before administration to assess the extent of the fetomaternal haemorrhage (FMH). If a significant FMH has occurred further doses of Rh D immunoglobulin should be given as directed from the results.

Antepartum:

A. First trimester (up to and including week 12 of gestation):

For the following potentially sensitising events:

- | | |
|---|---|
| <input checked="" type="checkbox"/> Miscarriage | <input checked="" type="checkbox"/> Termination of pregnancy |
| <input checked="" type="checkbox"/> Ectopic pregnancy | <input checked="" type="checkbox"/> Chorionic villus sampling |

An IMI dose of 250 IU CSL Rh D immunoglobulin should be offered to all Rh negative women with no preformed anti-D.

B. Beyond the first trimester (after week 12 of gestation)

A dose of **625 IU CSL Rh D immunoglobulin** should be offered to every Rh negative woman with no preformed anti-D to ensure adequate protection from immunisation for the following indications after 12 weeks gestation:

- genetic studies - fetal blood sampling
- chorionic villus sampling
- transplacental amniocentesis
- insertion of fetal amniotic shunts
- abdominal trauma sufficient to cause FMH (eg MVA, direct fall onto abdomen with evidence of soft tissue trauma)
- on each occasion of revealed or concealed antepartum haemorrhage
- external cephalic version, performed or attempted
- miscarriage or termination of pregnancy

As the evidence for efficacy of this dose for these indications is not available, it is recommended that, prior to administration, a sample should be taken from the mother for assessment of possible FMH. If a significant FMH has occurred further doses of Rh D immunoglobulin should be given as directed from the results.

C. Routine antenatal prophylaxis

As part of routine management all women should have a red cell antibody screen at booking and again at 28 weeks. All Rh negative primigravidae, who have no preformed anti-D, should receive antenatal prophylaxis at 28 and again 34 week's gestation using an IMI dose of **625 IU CSL Rh D immunoglobulin**.

Postpartum

All Rh D negative women, with no preformed anti-D, who deliver an Rh D positive infant should be offered Rh D immunoglobulin. It is recommended that the imported product, **WinRho 600 IU** be used for this indication. Prior to administration, a blood sample should be taken to determine if a significant FMH has occurred. However, the initial dose should not be delayed pending return of the results. Additional doses of WinRho should be administered if necessary as directed from the results.

Frequently asked questions

A number of workshops were held by CSL Bioplasma and ARCBS to assist in educating health professionals regarding the implementation of antenatal prophylaxis. Answers to a selection of common questions posed at these sessions are provided below. A full list of questions and answers can be found on the ARCBS website www.giveblood.redcross.org.au (under 'clinical information').

Will the implementation of antenatal prophylaxis be cost effective?

Antenatal prophylaxis is cost effective. The NHMRC Working Party for the Guidelines (1999)² commissioned a review of the available evidence on the prophylactic use of Rh D immunoglobulin in obstetrics and a review of the cost-effectiveness of Rh D immunoglobulin for a number of applications, including antenatal prophylaxis. Those results supported the efficacy and cost-effectiveness of Rh D immunoglobulin for antenatal sensitising events and antenatal prophylaxis.

Why was WinRho SDF™ imported?

The importation of WinRho SDF™ has allowed the commencement of a staged process towards full antenatal prophylaxis. The updated Guidelines³ state that such a product should continue to be imported in adequate quantities to support the staged introduction of universal antenatal prophylaxis until self-sufficiency is reached.

What is the risk of viral transmission with Rh D immunoglobulin and is WinRho SDF™ as safe as the Australian product?

There has never been a documented, verified case of viral transmission with either ARCBS/CSL Rh D immunoglobulin or WinRho SDF™ anywhere in the world.

Why was primigravidae chosen for antenatal prophylaxis?

The Guidelines^{2,3} detail the strategy that will allow the staged introduction of antenatal prophylaxis in the short term while working toward self-sufficiency in the longer term. The provision of Rh D immunoglobulin for primigravidae initially was in recognition of current availability of supply of product, and the fact that the average birth rate in Australia is less than two children per mother. The provision of antenatal prophylaxis for the first pregnancy provides cover for the next pregnancy.

What is the definition of primigravidae for this policy and should the first pregnancy of a subsequent partnership be classified as primigravidae for antenatal prophylaxis?

Primigravidae refers to women during their first pregnancy and is not dependent on subsequent partnerships. Women are regarded as primigravidae if they have had:

- a) any number of first or second trimester miscarriages; or
- b) any number of previous third trimester stillbirths.

Why were 28 and 34 weeks chosen as the time frames for the prophylactic administration of Rh D immunoglobulin?

Intrapregnancy immunisation is most likely to occur after the 28th week of gestation. For this reason 28 weeks was chosen as the timing for the first antenatal dose. As Rh D immunoglobulin is detectable in the patient's circulation for approximately 6 weeks, the timing of the second dose was recommended to be at 34 weeks. This should provide protection until delivery, when the postnatal dose is given if required. The Guidelines³ state that consideration could be given to investigating the appropriate dose of Rh D immunoglobulin at 28 weeks only as an alternative to a dose at both 28 and 34 weeks gestation.

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 Guidelines² 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 Guidelines³ 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).

What is the earliest time frame that an Rh D negative women 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 updated Guidelines³ recommend that Rh D immunoglobulin be given following therapeutic abortion, following curettage to remove products of conception and where bleeding occurs in an ongoing pregnancy both during the first trimester (up to and including 12 weeks gestation) and beyond the first trimester.

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.

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.

When should a FMH screen be performed?

For all potentially sensitising events that occur after the first trimester.

In this circumstance a maternal sample should be taken prior to administration of Rh D immunoglobulin, to assess the volume of FMH. However, at no time should a single dose of Rh D immunoglobulin be withheld based upon, or pending, the results to quantitate FMH.

What is the average size of a FMH?

About:

- 99% of fetal bleeds are less than 5 mL of red blood cells
- 50 % of bleeds are less than 0.05 mL
- 0.6% of bleeds may be higher than 30 mL

When should red cell antibody screening be performed?

The ANZSBT Guidelines for Blood Grouping and Antenatal Screening in the Prenatal and Perinatal Setting⁴ (see www.anzsbt.org.au) recommend that all pregnant women, both Rh D positive and Rh D negative, should be tested in the first trimester for blood group and clinically significant red cell antibodies. When no clinically significant antibodies are found the value of repeat testing at 28 weeks or later has been questioned⁵. However, repeat testing of Rh negative women at 28 weeks prior to administration of antenatal prophylaxis is becoming accepted protocol in most Australian centres, as is the elimination of the antibody screen at 34-36 weeks.

When should the blood sample for the red cell antibody screen be collected in relation to the administration of Rh D immunoglobulin at 28 and 34 weeks?

The blood sample must be taken before the administration of the antenatal Rh D immunoglobulin. It is acceptable for the Rh D immunoglobulin to be given immediately after the blood has been taken, before the results are available. This is because the vast majority of primigravidae women will not be sensitised and this is the most practical approach for optimising patient care.

Is it possible to distinguish between passively and actively acquired anti-D?

No that it why the patient's history and clinical notes on the request form are so important.

References

1. Bowman, J. The prevention of Rh immunization. *Transfusion Medicine Reviews* 1988; 129-150.
2. NHMRC Guidelines on the prophylactic use of Rh (D) immunoglobulin (anti-D) in obstetrics (1999).
3. NBA Guidelines on the prophylactic use of Rh (D) immunoglobulin (anti-D) in obstetrics (2003).
4. ANZSBT Guidelines for Blood Grouping and Antibody Screening in the Antenatal and Perinatal Setting. 2nd Edit 2004
5. Judd, W. (2001) Practice guidelines for prenatal and perinatal immunohaematology, revisited. *Transfusion* 41, 1450

Past Issues

<i>Issue Fifteen, 2003</i>	Laboratory Diagnosis for Infection with Human Immunodeficiency Virus (HIV)
<i>Issue Fourteen, 2003</i>	Hereditary Haemochromatosis Infectious Mononucleosis
<i>Issue Thirteen, 2003</i>	Thrombophilia Faecal Occult Blood Testing
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