# Guidelines for the use of Rh(D) Immunoglobulin (Anti-D) in obstetrics

This statement has been developed and reviewed by the Women's Health Committee and approved by the RANZCOG Board and Council.

A list of Women's Health Committee Members can be found in Appendix A.

Disclosure statements have been received from all members of this committee.

**Disclaimer** This information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances.

**First endorsed by RANZCOG: 1995**
**Current: July 2019**
**Review due: July 2024**

**Objectives:** To provide advice on the use of Rh (D) Immunoglobulin (Anti-D) in obstetrics.

**Target audience:** All health care professionals providing maternity care.

**Values:** The evidence was reviewed by the Women's Health Committee (RANZCOG) and applied to local factors relating to Australia and New Zealand.

**Background:** This statement was first developed for Australia by Women's Health Committee in 1995 and most recently reviewed in July 2019.

**Funding:** The development and review of this statement was funded by RANZCOG.

## *Table of contents*

## 1. Plain language summary

About one woman in seven has a Rh(D) negative blood group, and if her baby has a blood group that is Rh(D) positive there is a small risk that during pregnancy the baby's blood cells might stimulate an immune response in the mother's blood (sensitisation). If this happens and a woman makes antibodies against the D-positive blood group, there is a risk that a baby could be affected in this or future pregnancy. Giving anti-D to a woman who has a Rh(D) negative blood group during, or in the days following pregnancy can reduce the risk of sensitisation, and of adverse consequences in this and future pregnancies.

## 2. Summary of recommendations

| Recommendation 1 | Grade |
|---|---|
| All Rh (D) negative women (who have not actively formed their own Anti-D) should be offered Anti-D in the following clinical situations:<br><br>First trimester (dose 250 IU)<br>▪ Chorionic Villus Sampling;<br>▪ Miscarriage;<br>▪ Abortion (medical after 10 weeks of gestation or surgical); and<br>▪ Ectopic pregnancy.<br>▪ Molar pregnancy<br><br>There is insufficient evidence to suggest that a **threatened** miscarriage before 12 weeks gestation necessitates Anti-D. However, where the bleeding is repeated, heavy or associated with abdominal pain or significant pelvic trauma, immunoprophylaxis may be administered to women with no preformed anti-D antibodies (National Blood Authority Guidelines 2021).<br><br>Second and third trimester (basic dose 625 IU)<br>▪ Obstetric haemorrhage;<br>▪ Amniocentesis or other invasive fetal intervention;<br>▪ External cephalic version of a breech presentation, whether successful or not<br>▪ Abdominal trauma, or any other suspected intra-uterine bleeding or sensitising event.<br>▪ Abortion | C |
| **Recommendation 2** | **Grade** |
| All Rh(D) negative women (who have not actively formed their own Anti-D) should be offered a prophylactic dose of 625 IU at approximately 28 weeks gestation and again at approximately 34 weeks gestation. | B<br><br>Reference 4 |
| **Recommendation 3** | **Grade** |
| All women who deliver an Rh(D) positive baby should have quantification of fetomaternal haemorrhage to guide the appropriate dose of anti-D prophylaxis, and the dose should be given within 72 hours if possible. | B |
| **Good Practice Point** | **Grade** |
| Anti-D should be administered as a deep intramuscular injection. Among women with high BMI this may be most easily achieved using deltoid muscle. | Consensus-based recommendation |

| Rh antibody testing and assessing magnitude of feto-maternal haemorrhage | |
|---|---|
| **Recommendation 5** | **Grade** |
| Blood should be taken for Rh(D) antibody titre prior to administration of Anti-D, in order to detect those who have already become immunised. | Consensus-based recommendation |
| **Recommendation 6** | **Grade** |
| At 34 weeks gestation the test may be omitted if prophylactic Anti-D was given at 28 weeks. | Consensus-based recommendation |
| **Recommendation 7** | **Grade** |
| 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. | Consensus-based recommendation |
| **Recommendation 8** | **Grade** |
| If it is unclear whether the Anti-D detected in the mother's blood is passive or preformed, the patient record should be checked and/or treating clinician consulted to confirm whether Rh (D) immunoglobulin was administered during the pregnancy. If there is continuing doubt, Rh (D) immunoglobulin should be administered. | Consensus-based recommendation |
| **Recommendation 9** | **Grade** |
| All women who are given Anti-D in response to a potentially sensitizing event after the first trimester should have the magnitude of potential feto-maternal haemorrhage assessed and if necessary further Anti-D administered as appropriate. When more than four doses of anti-D are given and testing indicates that further anti-D will be required, consideration may be given to using the intravenous route for subsequent doses of anti-D. This will require anti-D specifically intended for intravenous usage (eg Rhophylac). | Consensus-based recommendation |

## 3. *Introduction*

In Australia and New Zealand the respective National Blood authorities have approved guidelines on the use of Rh-D immunoglobulin during pregnancy and the postpartum period. Fellows are recommended to view the Australian National Blood Authority Guidelines (2003) on the prophylactic use of Rh (D) immunoglobulin (Anti-D) in obstetrics at: http://www.blood.gov.au/system/files/documents/glines-anti-d.pdf and New Zealand Blood guidelines (2020) are available at: https://ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/NZBS_Use-of-Rh(D)-Immunoglobulin-During-Pregnancy-and-the-Post-Partum-Period.pdf?ext=.pdf

The documents aim to inform clinicians, other health professionals and policy makers about the most current recommendations for use of Anti-D in their country of practice. In addition, the National Blood Authority has published a Frequently Asked Questions about the use of Rh (D) immunoglobulin in collaboration with Royal Australian and New Zealand College of Obstetricians and Gynaecologists, Australian College of Midwives (ACM) ,Australian & New Zealand Society of Blood Transfusion (ANZSBT), Royal College of Pathologists of Australasia (RCPA), consumer representatives, Australian Red Cross Blood Service (Blood

Service), the New Zealand Blood Service (NZBS), National Blood Authority (NBA) and CSL Behring: https://www.nslhd.health.nsw.gov.au/Services/Directory/Documents/FAQs%20Use%20of%20Rh%20(D)%20Immunoglobulin.pdf

# 4. Discussion and recommendations

## 4.1 Overview

The administration of Rh (D) Immunoglobulin (Anti-D) has been shown previously (and more recently in Cochrane Reviews)[1, 2] to result in a significant reduction in the incidence of Rh isoimmunisation. The NHMRC has recommended the use of routine antenatal anti-D prophylaxis since 2002. [3] In New Zealand despite NZBlood guidelines supporting the routine administration of Rh (D) Immunoglobulin (Anti-D) at 28 and 32 weeks this has not become standard practice.

## 4.2 Evidence of benefit

Reviews in the Cochrane Library, Level 1, and undertaken by The National Institute for Clinical Excellence (NICE),[3] Level II and III, indicate that routine antenatal administration of Anti-D can result in a reduction in alloimmunisation of 78% (Cochrane Library, Level I evidence - 2 studies of 4500 women, both Level II) and 70% (NICE, Level II/III evidence - 4 studies of 6400 women, 1 Level II and 3 Level III).

The most robust evidence demonstrates Anti-D administration at a dose of 500IU at 28- and 34-weeks during pregnancy to all Rh (D) negative women (who have not actively formed their own Anti-D) will result in a reduction of alloimmunisation from about 1% to 0.35%.[4]

## 4.3 Product use

The following Rh(D) immunoglobulin products are manufactured by CSL: Immunoglobulin 250 IU (50mcg), Rh(D) Immunoglobulin VF 625 IU (125mcg), Rhophylac® 1500 IU (300mcg). In Australia all three are available, however Rhophylac 1500IU is not registered by Medsafe in New Zealand and therefore not available for general use.

Based on best evidence and current accepted practice, the following method of implementation is recommended:

~~All~~ Rh (D) negative women who have not actively formed their own Anti-D (unless NIPT at $11^{+0}$ weeks for fetal RHD has predicted that they are not carrying an Rh D positive fetus) should be offered Anti-D:

a) First trimester indications - CSL 250 IU (50mcg)
   i) Chorionic Villus Sampling;
   ii) Miscarriage;
   iii) Abortion (either medical after 10 weeks gestation or surgical); and
   iv) Ectopic pregnancy.
   v) Molar pregnancy

There is insufficient evidence to suggest that a threatened miscarriage before 12 weeks gestation necessitates Anti-D. However, where the bleeding is repeated, heavy or associated with abdominal pain or significant pelvic trauma, immunoprophylaxis may be administered to women with no preformed anti-D antibodies.

b) Second and third trimester indications - CSL 625 IU (125mcg)
   i) Obstetric haemorrhage;
   ii) Amniocentesis or other invasive fetal intervention;
   iii) External cephalic version of a breech presentation, whether successful or not; and
   iv) Abdominal trauma, or any other suspected intra-uterine bleeding or sensitising event.
   v) Abortion

c) All Rh (D) negative women (who have not actively formed their own Anti-D) should receive Anti-D immunoglobulin at approximately 28 weeks gestation and again at approximately 34 weeks gestation - CSL 625 IU (125mcg).

d) Post-natally, within 72 hours. All women who deliver an Rh (D) positive baby should have quantification of feto-maternal haemorrhage to guide the appropriate dose of anti-D prophylaxis.

Both medical and surgical methods of abortion are available in Australia and New Zealand. The evidence available to guide recommendations about use of anti-D for either medical or surgical termination of pregnancy is not particularly helpful, but there is theoretical evidence to suggest that the volume of feto-maternal haemorrhage in the first trimester might be enough to provoke maternal sensitisation. For this reason and because of the ready availability of anti-D and its excellent record of safety, as well as the problems associated with maternal sensitisation, RANZCOG follows the recommendations of RCOG that anti-D should be routinely offered for first trimester termination of pregnancy, whether by medical after 10 weeks gestation or surgical means.[5]

### 4.4 Rh antibody testing and assessing magnitude of feto-maternal haemorrhage

Blood should be taken for Rh(D) antibody titre prior to administration of Anti-D, in order to detect those who have already become immunised. However, at 34 weeks gestation, the test may be omitted if prophylactic Anti-D was given at 28 weeks gestation.

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 unsure whether the Anti-D detected in the mother's blood is passive or preformed, patient record should be checked and/or treating clinician consulted to confirm whether Rh (D) immunoglobulin was administered during the pregnancy. If there is continuing doubt, Rh (D) immunoglobulin should be administered.

All women as defined in paragraphs (b) and (d) should have the magnitude of potential feto-maternal haemorrhage assessed and, if necessary, further Anti-D administered as appropriate.

### 4.5. Cell-free DNA assessment of fetal Rh(D) genotype

Recent studies demonstrate the feasibility of using cell-free fetal DNA assessment to accurately determine the fetal Rh(D) genotype.[6] This knowledge can be used to determine which Rh(D)-negative women are potentially at risk of sensitisation from carrying a Rh(D)-positive fetus. The Australian National Blood Authority(2021) guidelines recommend NIPT for fetal RHD from 11+0 weeks of pregnancy because of higher test accuracy than at earlier weeks. This testing is not in routine clinical use in most jurisdictions currently.

These guidelines apply to those women who have not undergone fetal Rh(D) genotyping or who are predicted to be carrying a Rh(D)-positive fetus. Women who have been shown to be carrying a Rh(D)-negative fetus do not require anti-D prophylaxis either as routine or for potentially sensitising events.

## 5. References


1. Crowther CA, Keirse MJ. Anti-D administration in pregnancy for preventing rhesus alloimmunisation, Cochrane Database Syst Rev. 2000(2):CD000020.
2. Crowther C, Middleton P. Anti-D administration after childbirth for preventing Rhesus alloimmunisation, Cochrane Database Syst Rev. 2000(2):CD000021.
3. National Institute for Clinical Excellence (NICE). Guidance on the use of routine antenatal Anti-D prophylaxis for Rh (D) negative women. 2008. Available from: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12047.
4. Pilgrim, H., et al. (2009). "Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation." Health Technol Assess **13**(10): iii, ix-xi, 1-103.
5. Royal College of Obstetricians and Gynaecologists. The Management of Women with Red Cell Antibodies during Pregnancy. Green-top Guideline No. 65. 2014. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/rbc_gtg65.pdf
6. Chitty LS, Finning K, Wade A, Soothill P, Martin B, Oxenford K, et al. Diagnostic accuracy of routine antenatal determination of fetal RHD status across gestation: population based cohort study. *BMJ* 2014;**349**:g5243.


## 6. Other suggested reading

National Blood Authority
http://www.nba.gov.au/

https://www.blood.gov.au/anti-d-0

Australian Red Cross Blood Service (ARCBS)
To assist health professionals with the implementation of the new arrangements for antenatal prophylaxis, ARCBS and CSL Bioplasma have produced a range of educational materials that can be requested by faxing the CSL Immunotherapy Product Manager on 03 9358 5410.

Australian Red Cross and National Blood Authority Expert Panel Consensus Position Statement. Use of Rh(D) Immunoglobulin in Patients with a Body Mass Index >30.2015. Available from:
https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women's%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Consensus-Position-Statement-RhDIg-and-Women-with-High-BMI.pdf?ext=.pdf

New Zealand Blood Service (NZBlood)

NZ Blood guidelines (2013) are available at: https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/USE-OF-RH-D-IMMUNOGLOBULIN-DURING-PREGNANCY-AND-THE-POST-PARTUM-PERIOD-111G130.pdf

## 7. Links to other College statements

Consent and the provision of information to patients in Australia regarding proposed treatment (C-Gen 02a)
http://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20General/Consent-and-provision-of-information-to-patients-in-Australia-(C-Gen-2a)-Review-July-2016.pdf?ext=.pdf

Consent and provision of information to patients in New Zealand regarding proposed treatment (C-Gen 02b) https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20General/Consent-and-provision-of-information-NZ-(C-Gen-2b)-Review-March-2016_1.pdf?ext=.pdf

Evidence-based Medicine, Obstetrics and Gynaecology (C-Gen 15) https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20General/Evidence-based-medicine,-Obstetrics-and-Gynaecology-(C-Gen-15)-Review-March-2016.pdf?ext=.pdf

## 8. *Patient information*

A range of RANZCOG Patient Information Pamphlets can be ordered via: https://www.ranzcog.edu.au/Womens-Health/Patient-Information-Guides/Patient-Information-Pamphlets

NZBlood provides patient information on use of ant-D immunoglobulin at: https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/111I004.pdf

# *Appendices*

## Appendix A Women's Health Committee Membership

| Name | Position on Committee |
|---|---|
| Professor Yee Leung | Chair and Board Member |
| Dr Gillian Gibson | Deputy Chair, Gynaecology |
| Dr Scott White | Deputy Chair, Obstetrics |
| Associate Professor Ian Pettigrew | Member and EAC Representative |
| Dr Kristy Milward | Member and Councillor |
| Dr Will Milford | Member and Councillor |
| Dr Frank O'Keeffe | Member and Councillor |
| Professor Sue Walker | Member |
| Dr Roy Watson | Member and Councillor |
| Dr Susan Fleming | Member and Councillor |
| Dr Sue Belgrave | |
| Dr Marilyn Clarke | ATSI Representative |
| Associate Professor Kirsten Black | Member |
| Dr Thangeswaran Rudra | Member |
| Dr Nisha Khot | Member and SIMG Representative |
| Dr Judith Gardiner | Diplomate Representative |
| Dr Angela Brown | Midwifery Representative |
| Ms Ann Jorgensen | Community Representative |
| Dr Rebecca Mackenzie-Proctor | Trainee Representative |
| Prof Caroline De Costa | Co-opted member (ANZJOG member) |

## Appendix B Overview of the development and review process for this statement

*i. Steps in developing and updating this statement*

This statement was originally developed in 1995 and was most recently reviewed in July 2019. The Women's Health Committee carried out the following steps in reviewing this statement:

- Declarations of interest were sought from all members prior to reviewing this statement.
- Structured clinical questions were developed and agreed upon.
- An updated literature search to answer the clinical questions was undertaken.
- At the May 2019 teleconference, the existing consensus-based recommendations were reviewed and updated (where appropriate) based on the available body of evidence and clinical expertise. Recommendations were graded as set out below in Appendix B part iii)

*ii. Declaration of interest process and management*

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of the Women's Health Committee.

A declaration of interest form specific to guidelines and statements was developed by RANZCOG and approved by the RANZCOG Board in September 2012. The Women's Health Committee members were required to declare their relevant interests in writing on this form prior to participating in the review of this statement.

Members were required to update their information as soon as they become aware of any changes to their interests and there was also a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

There were no significant real or perceived conflicts of interest that required management during the process of updating this statement.

*iii. Grading of recommendations*

Each recommendation in this College statement is given an overall grade as per the table below, based on the National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades of Recommendations for Developers of Guidelines. Where no robust evidence was available but there was sufficient consensus within the Women's Health Committee, consensus-based recommendations were developed or existing ones updated and are identifiable as such. Consensus-based recommendations were agreed to by the entire committee. Good Practice Notes are highlighted throughout and provide practical guidance to facilitate implementation. These were also developed through consensus of the entire committee.

| Recommendation category | | Description |
|---|---|---|
| Evidence-based | A | Body of evidence can be trusted to guide practice |
| | B | Body of evidence can be trusted to guide practice in most situations |
| | C | Body of evidence provides some support for recommendation(s) but care should be taken in its application |
| | D | The body of evidence is weak, and the recommendation must be applied with caution |
| Consensus-based | | Recommendation based on clinical opinion and expertise as insufficient evidence available |
| Good Practice Note | | Practical advice and information based on clinical opinion and expertise |

## Appendix D Full Disclaimer

Purpose

This Statement has been developed to provide general advice to practitioners about women's health issues concerning anti D prophylaxis during pregnancy and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any person with a a need for anti D prophylaxis during pregnancy. It is the responsibility of each practitioner to have regard to the particular circumstances of each case. Clinical management should be responsive to the needs of the individual person with a breech presentation at term and the particular circumstances of each case.

Quality of information

The information available in Guidelines for the use of Rh(D) Immunoglobulin (Anti-D) in obstetrics is intended as a guide and provided for information purposes only. The information is based on the Australian/New Zealand context using the best available evidence and information at the time of preparation. While the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) had endeavoured to ensure that information is accurate and current at the time of preparation, it takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available. The use of this information is entirely at your own risk and responsibility.

For the avoidance of doubt, the materials were not developed for use by patients, and patients must seek medical advice in relation to any treatment. The material includes the views or recommendations of third parties and does not necessarily reflect the views of RANZCOG or indicate a commitment to a particular course of action.

Third-party sites

Any information linked in this Statement is provided for the user's convenience and does not constitute an endorsement or a recommendation or indicate a commitment to a particular course of action of this information, material, or content unless specifically stated otherwise.

RANZCOG disclaims, to the maximum extent permitted by law any responsibility and all liability (including without limitation, liability in negligence) to you or any third party for inaccurate, out of context, incomplete or unavailable information contained on the third-party website, or for whether the information contained on those websites is suitable for your needs or the needs of any third party for all expenses, losses, damages and costs incurred.

Exclusion of liability

The College disclaims, to the maximum extent permitted by law, all responsibility and all liability (including without limitation, liability in negligence) to you or any third party for any loss or damage which may result from your or any third party's use of or reliance of this guideline, including the materials within or referred to throughout this document being in any way inaccurate, out of context, incomplete or unavailable for all expenses, losses, damages, and costs incurred.

Exclusion of warranties

To the maximum extent permitted by law, RANZCOG makes no representation, endorsement or warranty of any kind, expressed or implied in relation to the materials within or referred to throughout this guideline being in any way inaccurate, out of context, incomplete or unavailable for all expenses, losses, damages and costs incurred.

These terms and conditions will be constructed according to and are governed by the laws of Victoria, Australia.