Category: Clinical Statement

Guidelines for the use of Rh(D) Immunoglobulin (Anti-D) in obstetrics (C-Obs 6)

This statement has been updated in response to updated evidence provided in the RANZCOG Clinical Guideline for Abortion Care in Australia and Aotearoa New Zealand. The interim update of the statement provides guidance on the use of Anti-D in the event of an abortion, and has been approved by the Women's Health Committee, RANZCOG Council and Board.

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

Conflict of Interest disclosures were received from all members of this Committee (Appendix B).

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 (Appendix C).

First developed by RANZCOG: 1995
Current version: July 2019 (interim update in November 2023)
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 to women[1].
Background:	The statement was first published in 1995 and reviewed in July 2019. The most recent interim update of this statement is to provide guidance on the use of Anti-D in the event of an abortion. The statement draws on earlier evidence-based methodology (i.e. not GRADE methodology), for approval by the Women's Health Committee in November 2023 (Appendix B).
Funding:	The development and review of this statement was funded by RANZCOG.

[1] *RANZCOG currently uses the term 'woman' in its documents to include all individuals needing obstetric and gynaecological healthcare, regardless of their gender identity. The College is firmly committed to inclusion of all individuals needing O&G care, as well as all its members providing care, regardless of their gender identity.*

Contents

1. Purpose and scope

The purpose of this statement is to provide advice on the use of Rh (D) Immunoglobulin (Anti-D) in obstetrics. It covers the clinical situations in which Anti-D should be offered in the first, second and third trimesters, the appropriate route of administration, and recommendations regarding Rh antibody testing and assessing magnitude of feto-maternal haemorrhage.

An interim partial update to the statement was undertaken in November 2023 to align with updated evidence presented in the RANZCOG Clinical Guideline for Abortion Care in Australia and Aotearoa New Zealand (2023).

2. 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.

3. Executive summary

This document discusses the use of Rh (D) Immunoglobulin (Anti-D) in Australia and Aotearoa New Zealand.

4. Table 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: First trimester (dose 250 IU) • Abortion (after 10 weeks of gestation for surgical or medical abortions); • Miscarriage; • Chorionic Villus Sampling; • Ectopic pregnancy;. • 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 (National Blood Authority Guidelines 2021). Second and third trimester (basic dose 625 IU) • Obstetric haemorrhage; • Amniocentesis or other invasive fetal intervention;	C

• External cephalic version of a breech presentation, whether successful or not • Abdominal trauma, or any other suspected intra-uterine bleeding or sensitising event. • Abortion	
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 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 (e.g., Rhophylac).	Consensus-based recommendation

5. 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 (2021) on the prophylactic use of Rh (D) immunoglobulin in pregnancy care at: https://blood.gov.au/anti-d-0 and New Zealand Blood guidelines (2023) are available at: https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/111G130.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/Documents/SDDocs/EPAS/FAQs%20Use%20of%20Rh%20%28D%29%20Immunoglobulin.pdf

6. Discussion and recommendations

6.1 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 NZ Blood guidelines supporting the routine administration of Rh (D) Immunoglobulin (Anti-D) at 28 and 32 weeks this has not become standard practice.

6.2 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]

6.3 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:

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) Abortion (after 10 weeks of gestation for medical or surgical abortions);
   ii) Miscarriage;
   iii) Chorionic Villus Sampling;
   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 Aotearoa New Zealand. Whilst the benefits of Anti-D for medical and surgical abortions under 10 weeks pregnant have not been clearly demonstrated in existing literature, and any risks in not giving it are unlikely to be significant, the benefits of not testing and administering Anti-D are significant to women and providers. There is a small risk of anaphylaxis associated with the administration of Anti-D. Requirement for Anti-D administration for surgical abortion may raise access issues, particularly for those who need to travel long distances, or who receive same-day abortion care.[5]

6.4 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.

6.5 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.

7. References

1. Crowther CA KM. Anti-D administration in pregnancy for preventing rhesus alloimmunisation. Cochrane Database Syst Rev. 2000;(2):CD000020.
2. Crowther C MP. 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.
4. Pilgrim H, Lloyd-Jones M, Rees A. Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation. Health Technol Assess. 2009;13(10):iii, ix-xi, 1-103.
5. RANZCOG. Clinical Guideline for Abortion Care: An evidence-based guideline on abortion care in Australia and Aotearoa New Zealand. 2023.
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.

8. Links to relevant College Statements and Guidelines

The RANZCOG Clinical Guideline for Abortion Care in Australia and Aotearoa New Zealand (2023)

Consent and the provision of information to patients in Australia regarding proposed treatment (C-Gen 02a)

Consent and provision of information to patients in New Zealand regarding proposed treatment (C-Gen 02b)

Evidence-based Medicine, Obstetrics and Gynaecology (C-Gen 15)

9. Links to relevant Clinical Guidelines

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

Australian Red Cross LifeBlood® assist health professionals with information on antenatal prophylaxis: https://www.lifeblood.com.au/health-professionals/clinical-practice/clinical-indications/HDFN

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://blood.gov.au/system/files/Expert-Panel-Consensus-Position-Statement-RhDIg-and-Women-with-High-BM-Final-12-June-2015.pdf

Aotearoa New Zealand Blood Service (NZ Blood): https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/111G130.pdf

10. Consumer resources

A range of RANZCOG Patient Information Pamphlets can be ordered via: https://www.ranzcog.edu.au/pip

NZ Blood provides patient information on use of Anti-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
Dr Scott White	Chair
Dr Anna Clare	Deputy Chair (Gynaecology) and Councillor
Associate Professor Amanda Henry	Deputy Chair (Obstetrics) and Councillor
Dr Samantha Scherman	Member and Councillor
Dr Marilla Druitt	Member and Councillor
Dr Kasia Siwicki	Member and Councillor
A/Professor Jared Watts	Member and Councillor
Dr Victoria Carson	Member - MFM
Dr Nisha Khot	Vice President and SIMG Representative
Dr Marilyn Clarke	Aboriginal and Torres Strait Islander Representative
Dr Angela Beard	He Hono Wahine representative
Dr Martina Mende	DRANZCOG representative
Dr Pallavi Desai	Specialist International Medical Graduate Representative
Professor Kirsten Black	Sexual & Reproductive Health Committee Representative
Dr Frank Clarke	State representative - Tasmania
Dr Elizabeth Gallagher	Territory representative - ACT
Dr James Brown	State representative - VIC
Dr Kathy Saba	State representative - QLD
Adrienne Priday	Midwifery Representative, New Zealand
Dr Angela Brown	Midwifery Representative, Australia
Ms Leigh Toomey	Community Representative
Dr Steve Resnick	Co-opted member: Neonatalologist

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

i. 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 RANZCOG Women's Health Committee or working groups.

A declaration of interest form specific to guidelines and statements was developed by RANZCOG and approved by the RANZCOG Board in September 2012. All members of the RANZCOG Guideline Development Group and Women's Health Committee 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.

ii. Steps in developing and updating this statement

This statement was developed in 1995 and was most recently reviewed by the Women's Health Committee in November 2023 in response to publication of the RANZCOG binational Clinical Guideline for Abortion Care. 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.
- In November 2023 the Women's Health Committee reviewed the updated statement out of session based on the available body of evidence in the clinical guideline and clinical expertise.

RANZCOG statements are developed according to the standards of the Australian 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 C: 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 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 need for anti D prophylaxis during pregnancy and the particular circumstances of each case.

Quality of information

The information available in this statement 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) has 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.

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

Version	Date of Version	Pages revised / Brief Explanation of Revision
v1.0	1995	The statement was first published.
V2.0	Nov / 2012	Routine review of the statement, approved by the RANZCOG Women's Health Committee/Board
V3.0	Jul / 2019	Routine review of the statement, approved by the RANZCOG Women's Health Committee/Board
V3.1	Jul / 2021	Minor update of the statement, approved by the RANZCOG Women's Health Committee/Board
V3.2	Nov / 2023	Interim update of the statement in response to publication of the RANZCOG binational Clinical Guideline for Abortion Care, approved by RANZCOG Women's Health Committee/Council.

Policy Version:	Version 3.2
Policy Owner:	Women's Health Committee
Policy Approved by:	RANZCOG Council/Board
Review of Policy:	July / 2024