South Australian Perinatal Practice Guideline

Anti-D Prophylaxis

Note:

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate, and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements, and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Note: The words woman/women/mother/she/her have been used throughout this guideline as most pregnant and birthing people identify with their birth sex. However, for the purpose of this guideline, these terms include people who do not identify as women or mothers, including those with a non-binary identity. All clinicians should ask the pregnant person what their preferred term is and ensure this is communicated to the healthcare team.

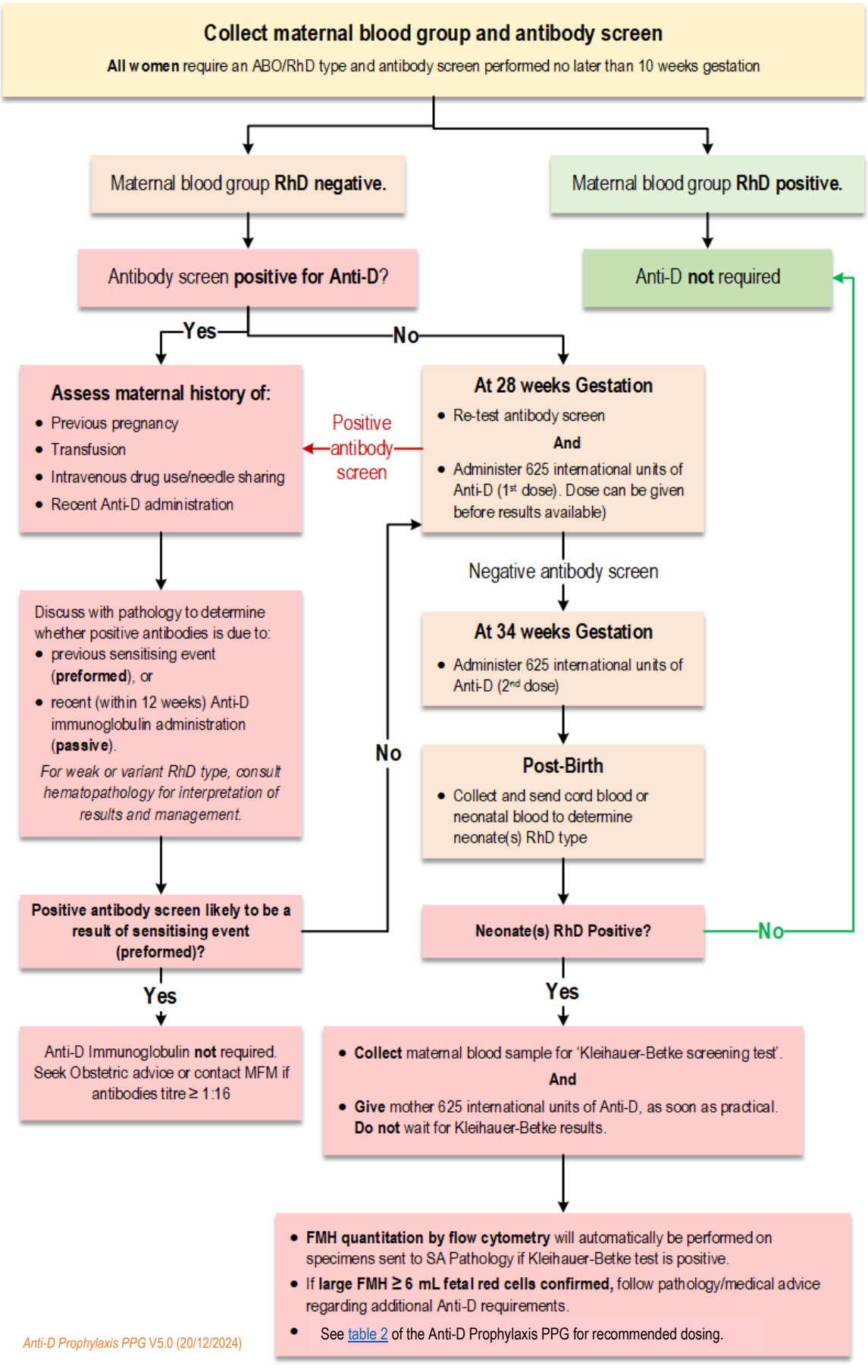
Explanation of the Aboriginal artwork:
The Aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the Aboriginal culture. The horseshoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horseshoe shape depicts a pregnant woman. The smaller horseshoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Australian Aboriginal Culture is the oldest living culture in the world, yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio-economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services, and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics, the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation, and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that perinatal services prepare to respectfully manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of PPG

The purpose of this guideline is to provide updated clinical guidance on the management of pregnancy in RhD Negative women. It includes guidance on Non-Invasive Prenatal Testing (NIPT) for fetal *RHD* and the administration of Rh(D) Immunoglobulin (Anti-D) prophylaxis. Anti-D is administered to manage pregnancies with the potential for isoimmunisation, through maternal-fetal transfusion.

Flowchart 1| Prophylactic Use of Anti-D in Pregnancy Pathway



Anti-D Prophylaxis PPG V5.0 (20/12/2024)

Flowchart 2| Additional Anti-D for Sensitising Events

Timing of Sensitising Event	Indications for Anti-D	Management
First trimester Up to 12+6 weeks gestation	• Threatened miscarriage where bleeding is heavy, repeated and or associated with abdominal pain or significant abdominal trauma • Confirmed miscarriage • Termination of pregnancy > 10 weeks gestation • Chorionic villus sampling (CVS) • Molar or ectopic pregnancy	**Give 250 international units of Anti-D***
Between 13 and 20 weeks gestation	• Genetic studies (CVS, amniocentesis and cordocentesis) • Abdominal trauma sufficient to cause FMH • Revealed or concealed antepartum haemorrhage (the possibility of concealed antepartum haemorrhage should be considered when unexplained uterine pain present) • miscarriage or termination of pregnancy • molar or ectopic pregnancy • intrauterine fetal death	**Give 625 international units of Anti-D*** *In cases where bleeding is ongoing an additional dose of Anti-D may be required at 6 weekly intervals.* *Seek Obstetric advice*
Beyond 20 weeks gestation	• As per indications for ***Anti-D between 13 and 20 weeks gestation*** (see above) • External cephalic version	• Collect maternal blood sample for Kleihauer-Betke screening test** • **Give 625 international units of Anti-D*** without waiting for results of FMH test → If large FMH ≥ 6 mL of fetal red red cells confirmed, follow pathology/MFM advice regarding additional Anti-D requirements See table 2 of the *Anti-D Prophylaxis PPG* for recommended dosing.

***Anti-D dose can be given beyond 72 hrs up to 10 days from sensitising event but may have lower efficacy**

**** FMH quantitation by flow cytometry will automatically be performed on specimens sent to SA Pathology if the Kleihauer-Betke test is positive**

Adapted from the National Blood Authority Guideline for the prophylactic use of Rh D immunoglobulin in pregnancy care.[1]

Table of Contents

Summary of Practice Recommendations

All women require ABO/RhD type and antibody screen performed prior to 10 weeks gestation.

Maternal blood group and antibody screen must be checked and documented prior to ordering and administering Rh(D) immunoglobulin (anti-D).

RhD Positive pregnant women do **not** require anti-D.

Anti-D must be given by deep intramuscular (IM) injection.

> The deltoid muscle or anterolateral thigh as the best site for administration of anti-D, with avoidance of the buttocks.

For women with a BMI > 30 kg/m^2, consideration should be given to factors which may impact the adequacy of the injection, including the site of administration and the length of the needle used.

> An increased dose and/or additional laboratory testing for women with a BMI > 30kg/m^2 is **not** recommended.

Anti-D 250 International Units (1st trimester) or 625 International Units (2nd & 3rd trimester) should be administered within 72 hours of a sensitising event for RhD Negative women.

> If anti-D has not been offered within 72 hours of a sensitising event, a dose given within up to 10 days may provide protection.

The Feto-maternal haemorrhage (FMH) screening test (Kleihauer-Betke) is recommended for sensitising events occurring beyond 20 weeks gestion and after birth. For public hospital patients, SA Pathology will perform FMH quantitation by flow cytometry automatically if the Kleihauer-Betke test is positive. Refer to 'Feto-Maternal Haemorrhage Assessment' section on page 9 of this guideline for further details.

Prophylactic Rh(D) Immunoglobulin-VF 625 International Units should be administered at 28 weeks and 34 weeks of pregnancy for RhD Negative women.

It is essential that the 28-week antibody screening blood sample is taken **before** the first routine prophylactic injection is given at 28 weeks.

Cord blood/heel prick testing for RhD is recommended on all neonates from RhD Negative mothers.

Rh(D) Immunoglobulin-VF 625 International Units should be administered within 72 hours post-birth unless the cord blood group is RhD Negative. Additional doses should be administered dependent on FMH test results.

Abbreviations

<	Less than
≤	Equal to or less than
>	Greater than
≥	Equal to or greater than
Anti-D	Rh(D) Immunoglobulin
BMI	Body mass index
CVS	Chorionic villus sampling
DAT	Direct Antiglobulin Test
FMH	Feto-maternal haemorrhage
HDFN	Haemolytic disease of the fetus and newborn
IM	Intramuscular
mL	Millilitre(s)
NIPT	Non-Invasive Prenatal testing
RhD	Rhesus D Antigen
Rh(D)	Rhesus D Immunoglobulin
RHD	Rhesus D *gene*

Definitions

Shared decision making	Shared decision making involves discussion and collaboration between a consumer and their healthcare providers. It is about bringing together the consumer's values, goals, and preferences with the best available evidence about benefits, risks and uncertainties of screening, investigations, and treatment, to reach the most appropriate healthcare decisions for that person.
Passive sensitisation	Developing positive antibodies due to receiving anti-D immunoglobulin within 12 weeks of positive result.
Preformed sensitisation	Developing positive antibodies due to previous sensitising event.

Background

In Australia, approximately 45,000 RhD negative women birth every year, with approximately two thirds carrying a RhD positive fetus.[2] Anti-D is administered to prevent RhD Negative women from developing antibodies against RhD positive fetal cells as a result of feto-maternal haemorrhage (FMH), thereby preventing isoimmunisation and its potential complications. While no maternal adverse effects occur in the mother, sensitisation may cause haemolytic disease of the fetus and newborn (HDFN) in subsequent pregnancies where the fetus is RhD positive.[1, 3] HDFN is a complex and potentially life threatening condition, causing fetal anaemia, and can lead to hyperbilirubinemia and jaundice.[3] In severe cases, HDFN can cause hydrops fetalis and kernicterus.[3]

Currently, all RhD Negative women are recommended to receive anti-D immunoglobulin, irrespective of the RhD status of their fetus. Recently, the National Blood Authority introduced recommendations for Non-Invasive Prenatal Testing (NIPT) for fetal *RHD* genotyping to enable targeted antenatal Rh(D) immunoprophylaxis, however this is **not** currently available in South Australia (SA).[1, 2] Therefore, universal Rh(D) immunoprophylaxis should be maintained until *RHD* NIPT is accessible.[1]

***Note**: Currently, there is no pathway for NIPT testing in SA. This guideline will be updated once there is more information about the availability of RHD NIPT in SA.*

Informed Consent

Women need to be informed that anti-D is a blood product, and should be given information on the potential risks and benefits to receiving it.[1] Written information should be provided, such as *You and your baby; important information for RhD negative women,* found under 'most popular resources' at www.lifeblood.com.au/health-professionals/learn/resource-library/featured-resources.

Woman may decline if the biological father of the fetus is known to be RhD Negative. Testing paternal RhD status may eliminate the need for antenatal prophylaxis, however, is **not** routinely recommended.

Aboriginal women should be referred to an Aboriginal Health Professional to support their care.

Contraindications

- In the obstetric setting anti-D should **not** be given to:
  - A RhD positive woman[1]
  - A RhD negative woman with preformed anti-D antibodies[1]

When maternal anti-D antibodies are detected, it is essential to determine whether the anti-D is preformed (by a maternal immune response to previous exposure to the RhD antigen) or passive (through recent administration of Rh(D) Immunoglobulin) to guide appropriate management of the pregnant woman and requires consideration of clinical history and laboratory findings.[1]

Note: *In cases of preformed anti-D antibodies, seek specialist obstetric advice and manage as sensitised.*[1]

Practice Points

- Anti-D must be given by deep IM injection.
- For women with a BMI > 30kg/m^2, particular consideration should be given to factors that may affect adequacy of the injection, including the site of administration and the length of the needle used.[1, 5]
  - An increased dose for women with a BMI > 30kg/m^2 is **not** recommended.[1, 5]
  - For women with a BMI > 30 kg/m^2 who experience a FMH of > 6 mL, consideration may be given to administering any required additional doses of Rh (D) immunoglobulin via the IV route (i.e. use of Rhophylac) to increase bioavailability and facilitate the more rapid clearance of fetal cells.[5]
- The dose required following a sensitising event is dependent on the gestation at the time of the event and by the magnitude of the FMH.
- For repeated sensitising events, a repeat dose may be appropriate after an interval of 6 weeks.[1]
- Doses that require IM injection volumes of > 5 mL should be divided and administered in separate IM injections in different sites.[1]

Indications

Sensitising Events in the First Trimester (up to and including week 12 of gestation)

- A dose of **250 International Units Rh(D) Immunoglobulin-VF** should be offered to every RhD Negative woman who has not actively formed their own anti-D antibodies and has a singleton or multiple pregnancy, to ensure adequate protection against isoimmunisation with the following indications:[1, 4]
  - threatened miscarriage where bleeding is heavy, repeated and/or associated with abdominal pain or significant abdominal trauma

    Note*: There is insufficient evidence to support the routine administration of anti-D for threatened miscarriage prior to 12 weeks gestation. However, in cases where bleeding is heavy, repeated and/or associated with abdominal pain or significant abdominal trauma Rh(D) may be given to women with no preformed anti-D antibodies.*[1]
  - confirmed miscarriage
  - ectopic pregnancy
  - termination of pregnancy (> 10 weeks gestation)

    Note: *There is insufficient evidence to recommend the use of anti-D in the setting of termination of pregnancy prior to 10 weeks gestation.*[1]
  - chorionic villus sampling (CVS)
  - molar pregnancy.

Sensitising Events in the Second and Third Trimester (from 13 weeks gestation)

- A dose of **625 International Units Rh(D) Immunoglobulin-VF** should be offered to every RhD negative woman with no preformed anti-D antibodies to ensure adequate protection against isoimmunisation for the following indications:
  - genetic studies (CVS, amniocentesis and cordocentesis)
  - abdominal trauma considered sufficient to cause FMH
  - each occasion of revealed or concealed antepartum haemorrhage (where the woman experiences unexplained uterine pain, the possibility of concealed antepartum haemorrhage should be considered)
  - external cephalic version (performed or attempted)
  - miscarriage or termination of pregnancy
  - ectopic pregnancy
  - molar pregnancy
  - intrauterine fetal death.
- In situations where bleeding is ongoing, an additional dose of anti-D may be appropriate at 6 weekly intervals.[1]
- Assessment of FMH is indicated for sensitising events occurring beyond 20 weeks gestation, with additional doses of Anti-D required for large volume FMH.[1]

Routine Antenatal Prophylaxis

- At **28 weeks** gestation and again at **34 weeks** gestation, a dose of **625 International Units Rh(D) Immunoglobulin-VF (anti-D)**, should be offered to women who are RhD Negative without preformed anti-D antibodies.
  - It is essential that women are screened for pre-existing anti-D before the prophylaxis is given at 28 weeks and that **the blood sample is taken before administration of anti-D.**
  - The result of the test does not need to be available before administration of anti-D.
  - No repeat screening is necessary before the second administration at 34 weeks (in cases where no sensitising events have occurred).
- Women who present > 28 weeks gestation with no antenatal care or have missed the 28-week dose, should have anti-D at the visit, making use of the opportunity.
  - Future doses can be adjusted to be administered 6 weeks after the first dose.

Aboriginal women should be referred to an Aboriginal Health Professional to support their care.

Management at Birth

Cord Blood Sampling

- A blood group and a Direct Antiglobulin Test (DAT) should be collected on all neonates born to a mother who:
  - is RhD Negative or;
  - has known clinically significant antibodies or;
  - has an unknown blood group and antibody status.

***Note**: Cord blood specimens are restricted to neonates aged < 24 hours*.

- If RhD Positive neonate:
  - collect a Kleihauer-Betke FMH screening test on all mothers who birth an RhD positive neonate (based on cord sample result)
  - neonate's blood group must be confirmed as RhD positive prior to the administration of the maternal postnatal prophylactic anti-D dose (postnatal prescription needed).

Postpartum Anti-D Administration

- A dose of 625 International Units should be offered to every RhD negative woman giving birth except when the baby is confirmed as RhD Negative.[1, 2, 6]
- Routine administration of antenatal anti-D does not prevent the postnatal prophylaxis administration to mothers who have a RhD positive neonate(s).
- Anti-D should not be given to women with pre-existing anti-D antibodies, except where this is known to be due to the presence of antenatally administered anti-D.
- A negative Kleihauer-Betke test result does not remove the need for prophylactic anti-D.

Note: *Anti-D must not be given to the neonate.*

Table 1: Summary of Recommendations for Anti-D Immunoglobulin Prophylaxis for RhD Negative Pregnant Women

Indications	Anti-D Dose
Obstetric conditions	
Sensitising event in the first trimester (up to 12^{+6} weeks gestation)	250 International Units
Sensitising event between 13- and 20-weeks' gestation	625 International Units
Sensitising event beyond 20 weeks gestation	625 International Units*
Antenatal prophylaxis	
28 weeks	625 International Units
34 weeks	625 International Units
Postpartum	
Birth of RhD positive baby	625 International Units*

**The dose is dependent on the result of the FMH screen (administer one vial 625 International Units whilst awaiting result of FMH screen). A postpartum FMH screen by Kleihauer-Betke test is considered optimal care and should be performed routinely following birth.*

Note: *FHM quantification by flow cytometry will automatically be performed on specimens sent to SA Pathology if Kleihauer-Betke test is positive.*

Feto-Maternal Haemorrhage (FMH) Assessment

The Kleihauer-Betke test is used as a screening test to detect clinically significant volumes of foetal blood in a maternal specimen. If the Kleihauer-Betke test is positive, flow cytometry is used to quantify foetal blood in a maternal specimen to guide anti-D dosing. If the Kleihauer-Betke test is negative, analysis by flow cytometry is not required. For all samples received by SA Pathology, a screening Kleihauer-Betke test will be performed. If this is positive, the sample will be reflexively assessed by flow cytometry.[6] FMH quantitation by flow cytometry results will be reported within 72 hours of sample collection.

For RhD negative women, a blood sample should be collected for FMH testing following:

- sensitising events **after** 20 weeks gestation
- after giving birth to a RhD positive baby
  - The optimal time to collect is 30 minutes after placental separation and preferably within the first hour after birth.

Anti-D 625 International Units is sufficient to cover FMH of up to 6 mL of RhD positive fetal red cells; accounting for 99% of FMH.[1]

For FMH volumes > 6 mL fetal red cells, an additional dose of anti-D is required and is calculated at 100 International Units per mL of fetal red cells more than 6 mL (covered by the initial 625 International Units dose). The required dose should be rounded up to the nearest full vial(s).[1]

See table 2 for guidance on additional anti-D dosing for large FMH ≥ 6 mL.

For large FMH volumes that require more than two IM injections, use of IV Rhophylac® 1500 International Units is recommended, calculated at 100 International Units per mL of fetal red cells more than 6 mL (covered by the initial 625 International Units dose).

Follow up testing should be performed on a sample collected 48 hours post IV anti-D or 72 hours post IM anti-D administration, to determine whether further dosing in required.

***Note**: FMH testing needs to occur prior to administration of anti-D. FMH testing is **not** required before 20 weeks gestation.*[1]

Table 2: Additional Anti-D Immunoglobulin Dosing for Large FMH ≥ 6 mL**

FMH volume (fetal red cells)	**Total Anti-D dose required**	***Give at the time of sensitising event/birth***	***Give when FMH volume is known***	
		Initial Anti-D dose (625[a] International Units) IM	**Additional Anti-D dose** (1 dose = 625 International Units) IM	**Rhophylac® dose** (1 dose = 1500 International Units) IV
< 6 mL	600 International Units	1	N/A	N/A
≥ 6 to < 12 mL	1200 International Units	1	1	N/A
≥ 12 to < 18 mL	1800 International Units (*choose either option 1* ***or*** *option 2*)[b]	1	2 (***option 1***)	N/A
			N/A	1 (***option 2***)
≥ 18 to < 21 mL	2100 International Units	1	N/A	1
≥ 21 to < 36 mL	3600 International Units	1	N/A	2
Specialist advice is recommended for any large FMH quantities and especially volumes ≥ 36 mL fetal red cells				
≥ 36 mL	Total Anti-D dose required = FMH volume x 100	1	N/A	Rhophylac® dose = Total Anti-D dose, minus 625, Divided by 1500 *Round up to nearest full number*

**Adapted from National Blood Authority. Guideline for the prophylactic use of RhD immunoglobulin in pregnancy care. Canberra, ACT 2024.

a) 625 international units covers FMH of up to 6 mL fetal red cells.
b) Two (2) vials of 625 IU can be administered as a single injection or as separate injections, however in either case to avoid discomfort associated with a larger volume IM injection or 2 additional injections, it may be more practical to offer IV Rhophylac® 1500 International Units.

Resources

SAPPGs Web-based App:
Practice Guidelines (sahealth.sa.gov.au)

Medicines Information: (sahealthlibrary.sa.gov.au)
https://sahealthlibrary.sa.gov.au/friendly.php?s=SAPharmacy

SA Health Pregnancy:
Pregnancy | SA Health

Australian Government Pregnancy, Birth and Baby: (www.pregnancybirthbaby.org.au)
Pregnancy, Birth and Baby | Pregnancy Birth and Baby (pregnancybirthbaby.org.au

Pathology Tests Explained: (https://pathologytestsexplained.org.au/)
Pathology Tests Explained

Lifeblood:
Featured resources | Lifeblood

Rh D Consumer Leaflet:
RhD IMIG CMI (cslbehring.com)

References

1. National Blood Authority. Guideline for the prophylactic use of Rh D immunogobulin in pregnancy care. Canberra, ACT2024. Available from: https://www.blood.gov.au/guideline-prophylactic-use-rh-d-immunoglobulin-pregnancy-care.
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5. National Blood Authority. Expert Panel Consensus Position Statement regarding the Use of Rh(D) Immunoglobulin in Patients with a Body Mass Index > 30. 2015.
6. Australian and New Zealand Society of Blood Transfusion. Guidelines for Laboratory Estimation of Fetomaternal Haemorrhage, 2nd Ed. September 2021.

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19/04/2016	V4	SA Health Safety & Quality Strategic Governance Committee	Reviewed.
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