

USE OF RH D IMMUNOGLOBULIN (Anti-D Immunoglobulin) DURING PREGNANCY AND THE POST PARTUM PERIOD

REASON FOR ISSUE: Address DCR38730 and drop the volumes of fetal whole blood and only refer to fetal red cell volumes.

The guidelines for use of Anti-D Immunoglobulin have been prepared by the New Zealand Blood Service (NZBS) for use by midwives and medical practitioners involved in the care of pregnant women and obstetric practice in New Zealand. They provide information on:

- 1) Dose and indications for the use of Anti-D Immunoglobulin (p1 - 3).
- 2) Critical timing issues for red cell antibody screening and antenatal or postnatal use of Anti-D Immunoglobulin (p1 - 3).
- 3) Additional doses of Anti-D Immunoglobulin (p1-3)
- 4) Assessment of fetomaternal haemorrhage (FMH) (p2 - 4).
- 5) Summary of the current Clinical Practice Guidelines (p3 - 6)
- 6) Where a woman decides not to receive Anti-D Immunoglobulin (p6)
- 7) Concerns regarding the safety of Anti-D immunoglobulin (p7)

Definitions

In this document the term *Anti-D Immunoglobulin* refers to the therapeutic injection (blood product) containing the RhD antibody; the term *anti-D* refers to pre-formed RhD antibodies present in an affected (immunised) woman. The *red cell antibody screen* is part of *group and screen* test.

Dose and Indications for the Use of Anti-D Immunoglobulin

All RhD negative woman (who have not actively formed their own anti-D antibodies) should normally be offered Anti D Immunoglobulin in the following circumstances:

Dose of Anti-D Immunoglobulin	Indications
<p>Up to & including 12 weeks gestation (1st trimester) in an RhD negative woman:</p> <p>Anti-D Immunoglobulin 250 IU for single pregnancy</p>	<ul style="list-style-type: none"> • Termination of pregnancy medical from 10-12 weeks of gestation or surgical) • Spontaneous miscarriage • Ectopic pregnancy • Chorionic villus sampling • Molar pregnancy • Uterine bleeding where this is repeated, heavy or associated with abdominal pain <p>Notes</p> <ol style="list-style-type: none"> 1. There is insufficient evidence to recommend the use of Anti-D Immunoglobulin for threatened miscarriage before 12 weeks. 2. Only limited evidence exists for Anti-D prophylaxis before 12 weeks gestation, but theoretical grounds exist for a sufficient volume of fetal red cells to enter the maternal circulation and immunise the mother during a miscarriage, medical termination from 10-12 weeks or surgical termination of pregnancy. Prophylaxis is therefore recommended after these events. 3. A blood sample should normally be collected before administration of Anti-D to confirm that the mother has not been immunised and made their own anti-D. 4. For a multiple pregnancy, the dose of Anti-D Immunoglobulin should be increased to 625 IU. 5. Anti-D should be offered and administered within 72 hours of any event listed above. 6. Kleihauer testing is not required before 20 weeks gestation.

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<p>Weeks 12 - 40+ gestation (2nd and 3rd trimesters) in an RhD negative woman:</p> <p>Anti-D Immunoglobulin 625 IU, if any of the following potentially sensitising events have occurred:</p>	<ul style="list-style-type: none"> • Miscarriage or threatened miscarriage • Antepartum haemorrhage • Intrauterine death or stillbirth • External cephalic version • Chorionic villus sampling • Ectopic pregnancy • Molar pregnancy • Termination of pregnancy (either medical or surgical) • Abdominal trauma sufficient to cause FMH • Amniocentesis, chorionic villus sampling, and intrauterine fetal blood sampling • In utero therapeutic procedures (transfusion, surgery, insertion of shunts, laser) <p>Notes</p> <ol style="list-style-type: none"> 1. The standard dose of Anti-D Immunoglobulin is 625 IU, administered within 72 hours. If Anti-D is not given within 72 hours, administration within 10 days may provide some benefit. 2. A Kleihauer test is not indicated before 20 weeks of gestation. After 20 weeks gestation it is used to identify events where increased fetomaternal bleeding has occurred and an increased dose of Anti-D is indicated. 3. If the Kleihauer test report recommends a dose greater than two (2) vials of Anti D Immunoglobulin, the dose must be discussed with a Transfusion Medicine Specialist. They will confirm the dose and determine if an IV preparation is more appropriate, including the correct rate of administration for an IV dose. 4. If the fetal blood group shows anomalous results for RhD it should be regarded as RhD positive, until confirmed. 5. Where bleeding continues after 12 weeks gestation, Anti-D Immunoglobulin should be given at up to two (2) weekly intervals.
<p>Routine Antenatal Anti-D Prophylaxis (RAADP):</p> <p>Two-dose RAADP: Anti-D Immunoglobulin 625 IU at 28 and 34 weeks gestation</p>	<p>Important:</p> <p>Before administration of the 28 week dose a blood sample must be taken for a red cell antibody screen. There is no need to wait for the test result before administration of the Anti-D immunoglobulin. An antibody screen is not required before the 34-week dose as residual antibody will be present from the first dose.</p> <p>Notes</p> <ol style="list-style-type: none"> 1. One-dose RAADP: There may be situations where only a single dose can be provided. In these situations, two (2) vials of Anti-D 625 IU are given at 30 weeks after a red cell antibody screen blood sample has been taken. 2. If anti-D antibodies are detected in the sample taken before administration, you must contact a Transfusion Medicine Specialist to discuss management. 3. Post-partum prophylaxis is still required for sensitising events after use of RAADP. 4. Further red cell antibody screening is not indicated for women who have received routine prophylactic Anti-D, unless fetal anaemia is suspected.

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<p>Post-partum prophylaxis in an RhD negative woman who has given birth to an RhD positive baby:</p> <p>Anti-D Immunoglobulin 625 IU</p> <p>Additional dose(s) are indicated dependent on the red cell volume of the fetomaternal haemorrhage.</p>	<p>Note: Prior routine antenatal Anti-D prophylaxis (RAADP) or prophylaxis for an antenatal sensitising event does not preclude post-partum prophylaxis.</p>
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Clinical Practice Guidelines

Red cell antibody screening & Routine Antenatal Anti-D Prophylaxis (RAADP)

1. Collect the blood test samples for routine red cell antibody screening at 27-28 weeks gestation **before the injection of prophylactic Anti-D immunoglobulin.**
There is no need to wait for the antibody screen results before administration of the Anti-D Immunoglobulin.
2. **If the blood sample for red cell antibody screening is collected after injection of prophylactic Anti-D Immunoglobulin,** the antibody screen is likely to be positive due to the Anti-D Immunoglobulin injected. It is not possible to distinguish between injected Anti-D Immunoglobulin and anti-D produced by immunisation (sensitisation), by testing a single blood sample. The following will be appropriate:
 - a. The woman should continue to have two-weekly monitoring of the antibody titre until the end of the pregnancy, or such time as a Transfusion Medicine Specialist indicates otherwise.
 - b. Specialist Obstetric advice should be obtained on monitoring of the fetus for the remainder of the pregnancy, and
 - c. Ongoing consultation with a Transfusion Medicine Specialist will be required to evaluate the series of antibody titre tests. Appropriately timed tests over the following 4-12 weeks will clarify whether or not immunisation has occurred or whether the passively injected prophylactic Anti-D Immunoglobulin was responsible for the positive red cell antibody screen and the detection of anti-D.
3. At the time of delivery, if any uncertainty exists over whether or not immunisation of the mother to RhD has occurred (i.e. whether or not the mother is producing anti-D), a Transfusion Medicine Specialist should be consulted promptly for advice on whether prophylactic Anti-D Immunoglobulin administration is indicated.
4. If Anti-D Immunoglobulin has not been offered within 72 hours, a dose given within 10 days may provide some protection.

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Assessment of the size of fetomaternal haemorrhage

1. The recommended doses of Anti-D Immunoglobulin (p1-2) are sufficient to cover the maximum fetomaternal bleed before 20 weeks gestation; testing to determine the size of fetomaternal haemorrhage is not required.
2. After 20 weeks gestation the size of any fetomaternal haemorrhage should be assessed following any potentially sensitising event.
3. Assessment of the size of any fetomaternal haemorrhage should be completed promptly so that any Anti-D Immunoglobulin prophylaxis can be completed within 72 hours of the sensitising event.
4. The patient's body weight may also affect interpretation of the test result. Where the lean body weight exceeds 100kg an additional dose may be appropriate.
5. Consultation with a Transfusion Medicine Specialist is recommended when more than 1250 IU Anti-D Immunoglobulin (two vials) appears to be indicated by a Kleihauer test, to ensure interpretation of the information is correct.
6. Other tests for quantifying fetomaternal haemorrhage exist, e.g. FLOW cytometry, but are not widely available.
7. A negative Kleihauer test does **not** remove the need for Anti-D.
8. If a dose of Anti-D Immunoglobulin greater than two 625 IU vials is required, an intravenous (IV) product may be considered.
 - a. The maximum recommended intravenous dose administration rate is 3000 IU 8 hourly
 - b. Rate of administration of the current New Zealand IV product, Rhophylac (1500 IU in a pre-filled syringe) is 2mL per 15 - 60 seconds as an IV bolus. No greater than 2mL per 60 seconds can be administered.
 - c. Controlling the dose size and infusion rate is needed to reduce the risk of an adverse reaction in the woman during the rapid clearance of fetal D positive red cells.
 - d. Monitor the new-born's haemoglobin if a large FMH detected.
9. If an intramuscular product is used, it is recommended that large volumes (greater than 5mL) should be administered in divided doses at different sites. Ensure the site chosen will allow the injection to reach the muscle.
10. For FMH of ≥ 6 mL of fetal red cells follow-up testing is recommended to monitor adequate clearance of fetal cells. Collection and testing of a repeat sample should be made within 72 hours of intramuscular administration or 48 hours of intravenous administration of Anti-D immunoglobulin. Contact the Transfusion Medicine Specialist for advice if the result suggests further Anti-D may be indicated. This cycle may need to be repeated until fetal red cells are no longer detected.

Minimum immunising dose of fetal red cells

The minimum volume of RhD positive red cells that will immunise an RhD negative woman to make anti-D antibodies is of the order of 0.10-0.25 mL.

Dose of Anti-D Immunoglobulin

1. A dose of 625 IU will protect against a fetomaternal haemorrhage of 6 mL of fetal red cells. There is no evidence that a larger dose is more effective for bleeds less than 6mL of fetal red cells. (*extrapolated from* Pollack W, et al. Transfusion (1971) 31:288-9)
2. Where a Kleihauer (or other) test indicates that a fetomaternal haemorrhage exceeds 6mL of fetal red cells optimal prophylaxis requires that additional doses of Anti-D Immunoglobulin should be offered, as determined by the test result.
3. A dose of 250 IU Anti-D Immunoglobulin will protect against first trimester sensitising events in single pregnancies.

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Route of injection

1. Anti-D Immunoglobulin should be given as instructed by the manufacturer, except as specified in (2) of this section. A product listed as being suitable for intravenous injection may be given by intravenous or intramuscular injection. A product listed as being suitable for intramuscular injection is intended for administration by this route; it **must not** be given intravenously.
2. Whilst there is some evidence to suggest that intramuscular administration of Anti-D Immunoglobulin may be associated with an increased risk of lack of effect in patients with a BMI >30, there is currently insufficient evidence to support a change to clinical and laboratory practice at the present time. A Consensus Statement by an expert panel convened by The Australian Red Cross Blood Service and the National Blood Authority (Australia) in 2015 recommends that for women with a BMI ≥30, particular consideration should be given to factors which may impact on the adequacy of the injection, including site of administration and the length of the needle used. In addition, for women with a BMI ≥30 who experience a FMH of greater than 6mL of fetal red cells, consideration may be given to administering any additional required doses of Anti-D Immunoglobulin via the intravenous route (i.e. use of Rhophylac), to increase bioavailability and facilitate the more rapid clearance of fetal cells.
3. Women who have a moderate or severe thrombocytopenia should not receive intramuscular injections. In this situation a product suitable for intravenous administration should be administered intravenously.

Antenatal Sensitising Events

1. Fetomaternal haemorrhage has been demonstrated following the events listed on pages 1 and 2.
2. The RhD blood group has been detected on fetal red cells at about 6 weeks gestation.
3. Evidence exists for a risk of immunisation following surgical abortion, ruptured ectopic pregnancy and amniocentesis.
4. There is conflicting evidence on whether a significant risk for immunisation arises after threatened miscarriage or spontaneous miscarriage without curettage.
5. Quantified data on risk for RhD immunisation following first trimester events is not available; the risk may be less than that associated with the birth of an RhD positive fetus to an RhD negative woman.
6. It has been common practice in New Zealand, and elsewhere, to use Anti-D Immunoglobulin for the purposes listed on pages 1 and 2 because of the potential risk for fetomaternal haemorrhage.
7. No formal evidence exists on the benefit of Anti-D Immunoglobulin after trauma in pregnancy, or for prophylaxis after antepartum haemorrhage. However, it is routine practice to use Anti-D Immunoglobulin for these indications because of the risk for significant fetomaternal haemorrhage occurring.
8. There is a lack of published information on the views of women about use of Anti-D Immunoglobulin for these purposes.
9. There is no demonstrated evidence of harm to the fetus in the studies performed on the use of Anti-D Immunoglobulin for antenatal sensitising events.

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Routine antenatal Anti-D prophylaxis (RAADP) for women who are RhD negative

Occasional cases of RhD immunisation are known to occur in RhD negative women in late pregnancy (approximately 1% of women who have an RhD positive fetus). Most cases occur after 28 weeks gestation, and about 60% of these can be prevented by routine antenatal Anti-D prophylaxis (RAADP).

1. There is considerable observational evidence but no high level evidence to support the use of RAADP.
2. RAADP for RhD negative women is now an accepted clinical practice in many western countries. RAADP is recommended in guidelines in these countries.
3. Published studies on the safety of RAADP have evaluated only a limited range of outcome parameters and have found no adverse effects. Comprehensive assessments of fetal survival and growth, neonatal morbidity, mortality and immunological status have not been undertaken.
4. A small percentage of women may be immunised to make anti-D, either before 28 weeks gestation, or despite use of RAADP. If this occurs, a woman is likely to have a high rising titre of anti-D in her blood. The red cell antibody screening tests at 28 (or 30) week's gestation, obtained before the injection of RAADP Anti-D Immunoglobulin will detect immunisation events before this test.
5. On rare occasions a woman may still be accidentally immunised, either before 28 weeks gestation, or despite the use of RAADP. If this occurs, the woman will show the presence of a high or rising titre of anti-D in her plasma. The red cell antibody screening tests at 28 weeks gestation, prior to administration of the 28 week dose of Anti-D Immunoglobulin, is designed to detect prior immunisation events.
6. Antibody screening is not carried out routinely after RAADP has been started because small amounts of anti-D will persist from this treatment until the birth of the fetus. Distinguishing the treatment antibody from immune (pre-formed) anti-D made by the woman is not straightforward. It will usually require repeat antibody screens and antibody titres to be performed and an NZBS Transfusion Medicine Specialist to interpret the results.
7. **Where the person managing a pregnancy is concerned about a potential sensitising (immunising) event(s) or the progress of the pregnancy including possible fetal anaemia, a red cell antibody screen should be requested and will usually need to be repeated two-weekly to evaluate changes in antibody titre. NZBS Transfusion Medicine Specialists are available to assist with interpreting the test results.**
8. Further information on the clinical and cost-effectiveness of RAADP is available, refer to: Pilgrim H, Lloyd-Jones M, Rees A. *Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation*. Health Technology Assessment. 2009;**13** (10) (Source: PubMed).

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Circumstances where a woman decides not to accept Anti-D Immunoglobulin prophylaxis

The clinician should ensure that each RhD negative woman has accurate information about the risk from anti-D immunisation, its potential adverse effects and the benefits from the prophylactic use of Anti-D Immunoglobulin.

NZBS information leaflets on Anti-D Immunoglobulin, Routine Antenatal Anti-D Prophylaxis and Blood Group Antibodies & Haemolytic Disease of the Fetus and Newborn are available at www.nzblood.co.nz and from the Blood Banks across NZ.

The following comments are offered as a guide on relevant information that should be available where a woman declines to accept Anti-D Immunoglobulin.

Father is believed to be RhD negative:

Some RhD negative women decline to accept Anti-D Immunoglobulin if a test on the father of the fetus/infant has shown an RhD negative result. Where this situation arises a clinician should take reasonable steps to ensure that:

1. The possibility for the father of the fetus/infant to have weak expression of RhD has been excluded. Routine laboratory testing of specimens from patients will not normally detect the presence of weak D; additional tests for weak D on a paternal sample will be required.
2. The test for RhD type should normally be performed on two separate samples before it is regarded as confirmed.

The woman indicates that she will not have any more children:

Some RhD negative women who do not wish to have any more children make a decision not to receive Anti-D Immunoglobulin. Where this arises it is recommended that the woman should understand that:

1. Unplanned pregnancies may occur and could be affected if she forms anti-D. The chance for making anti-D after each normal RhD positive pregnancy is about 8%.
2. RhD negative blood donors are uncommon in geographic areas that have a low proportion of Europeans in the population. If a woman is immunised and makes anti-D following pregnancy, and later travels to, or lives in, parts of Asia or Africa in particular, there may be difficulty and delay in providing blood transfusion for her in most countries on these continents.

Information on the safety of the Anti-D Immunoglobulin products available in NZ

Information on the safety and potential risks of Anti-D Immunoglobulin products must be provided to all potential recipients. The following is a short summary of key issues.

1. Blood donations are always tested for the infections: HIV / AIDS, syphilis, hepatitis B and hepatitis C. Blood donations are only used if there is no evidence of these infections. The process for making Anti-D Immunoglobulin is able to destroy these and many other viruses.
2. There is no evidence that the Anti-D Immunoglobulin injection used in NZ has ever spread any important infections, including HIV/AIDS or hepatitis.
3. As Anti-D Immunoglobulin is a blood product, it could possibly pass on some infections, although the risk of this happening is very low.
4. Anti-D Immunoglobulin supplied in New Zealand is now obtained from North American donors. Blood donors in North America are always checked for health and lifestyle whenever they give blood. A blood donation is only collected if a donor is in good health and does not have any condition detectable by the standard donor screening process that could be passed on by Anti-D.
5. There is no evidence that either classical CJD (Creutzfeldt Jakob Disease) or variant CJD which occurred in the UK and Europe in the 1990's has ever been transmitted by manufactured blood products such as Anti-D Immunoglobulin.
6. An allergic reaction may occur after injection of blood products, including Anti-D Immunoglobulin, though this is rare (less than once each year in New Zealand).