USE OF RH-D IMMUNOGLOBULIN DURING PREGNANCY AND THE POST PARTUM PERIOD

The Guidelines for use of Anti-D Immunoglobulin have been prepared by NZ Blood Service for use by Midwives and Medical Practitioners involved in caring for pregnancies or obstetric practice in New Zealand. They provide information on:

INDICATIONS FOR USE OF ANTI-D IMMUNOGLOBULIN

Anti-D Immunoglobulin should normally be offered in the following circumstances:

Timing of Anti-D	Indication
1. Antenatal obstetric indications *(i.e. after sensitising events)*	1.1 An Rh D negative woman who has had any of the following: • Surgical management of miscarriage • Surgical termination of pregnancy • Ectopic pregnancy • Invasive procedures involving chorion villus sampling, amniocentesis or intrauterine blood sampling • External cephalic version 1.2 NZBS recognises that definitive studies to support the use of anti-D have not been performed for the following conditions. NZBS also recognises that fetomaternal haemorrhage is known to occur in these conditions and current international practice supports the use of anti-D for *clinically appropriate cases of*: • Threatened miscarriage (before 20 weeks) • Spontaneous miscarriage • Abdominal trauma • Antepartum haemorrhage **Anti-D Immunoglobulin dose:** ○ **250IU for single pregnancy events in the first trimester (up to 12 wks)** ○ **600-625IU for multiple pregnancy events up to 12 weeks** ○ **600-625IU for any pregnancy event after 12 weeks** Note: prior routine antenatal prophylaxis does not preclude prophylaxis for sensitising events or vice-versa
2. Routine Antenatal Prophylaxis	An Rh D negative woman who is pregnant, has not previously been immunised to produce anti-D; one dose at each of 28 and 34 weeks gestation. **Anti-D Immunoglobulin dose: 600-625IU**
3. Postpartum Prophylaxis	An Rh D negative woman who gives birth to an Rh D positive infant and who is not already immunised to make anti-D. **Anti-D Immunoglobulin dose: 600-625IU (additional dose(s) are indicated where fetomaternal haemorrhage is greater than 6ml fetal red cells (i.e. 12mL fetal blood))** Note: prior routine antenatal prophylaxis or prophylaxis for sensitising events does not preclude postpartum prophylaxis

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CLINICAL PRACTICE GUIDELINE

Definitions: in this document the term: Anti-D Immunoglobulin refers to the therapeutic injection product containing this antibody; the term anti-D refers to antibody present in an affected person.

Blood Group Antibody Screening & Routine Antenatal Use of Anti-D Immunoglobulin

1. Collect the blood test samples for routine antibody screening at 27-28 weeks gestation ***before injection of prophylactic Anti-D***.
    a. If the antibody screen is negative, administer Anti-D Immunoglobulin 600 – 625 IU
    b. If circumstances do not permit a delay after collecting the test sample, administer Anti-D Immunoglobulin and await the test result.
2. If the blood sample for 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 specimen. 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 antibody screen and detection of anti-D.
3. At the time of delivery, if any uncertainty exists over whether or not immunisation of the mother to Rh D 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.

First trimester (before 12 weeks) obstetric events

1. **Spontaneous abortion** - without a need for surgical intervention: Clinical practice varies as the risk for immunisation to make anti-D is very low. A 250IU dose of anti-D is available.
2. **Induced abortion and spontaneous abortion where curettage is performed**: A risk for immunisation to make anti-D exists and a 250IU dose of anti-D is recommended.
3. **Threatened miscarriage:** A small risk for anti-D immunisation exists; a 250IU dose of Anti-D Immunoglobulin is available for single pregnancies and 600-625IU for multiple pregnancies. The pregnancy should be dated by ultrasound.

Antenatal haemorrhage and other obstetric events requiring a further dose of Anti-D

Where a woman who has had a dose of Anti-D Immunoglobulin has a subsequent risk event for immunisation, the following is recommended:

1. If the previous dose was given 2 weeks or more previously a further dose of Anti-D Immunoglobulin should be offered.
2. Where the previous dose was given less than 2 weeks previously a further dose of Anti-D Immunoglobulin should only be offered if the pregnancy is more than 20 weeks gestation and the size of the fetomaternal bleed is likely to be greater than 12ml of blood (6ml red cells) in total.
3. Anti-D Immunoglobulin should be given to all non-sensitised RhD negative women with a threatened miscarriage after 12 weeks of pregnancy. Where bleeding continues intermittently after 12 weeks' gestation, anti-D Ig should be given at 2-weekly intervals

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Timing of Anti-D Immunoglobulin administration after an immunising event (antenatal event or birth)

1. Anti-D Immunoglobulin prophylaxis should be given as soon as possible and always within 72 hours of an immunising event.
2. If Anti-D Immunoglobulin has not been offered within 72 hours a dose given within 10 days *may* provide some protection.

Assessment of the size of fetomaternal haemorrhage

1. The recommended doses of Anti-D Immunoglobulin (p 1) are sufficient to cover the maximum fetomaternal bleed before 20 weeks gestation; testing to determine the size of fetomaternal haemorrhage is not required.
2. It is appropriate to assess the size of fetomaternal haemorrhage after 20 weeks gestation.
3. Assessment of the size of any fetomaternal haemorrhage should be completed promptly so that any anti-D prophylaxis can be given within 72 hours of the immunising event.
4. Although the Kleihauer test can detect a fetomaternal haemorrhage of 0.1ml or less, false positive results and problems of specificity exist with this test. The test is less reliable during the first two trimesters of pregnancy due to increased levels of fetal haemoglobin in maternal red cells at this stage of pregnancy. Comparative studies of laboratory performance have shown significant variation in performance of the Kleihauer test. Clinicians using the test should be aware of limitations in its use.
5. 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.
6. Consultation with a Transfusion Medicine Specialist is recommended where more than 1200-1250 IU Anti-D Immunoglobulin (two vials) appears to be indicated by a Kleihauer test, to ensure interpretation of the information is correct.
7. Other tests for quantifying fetomaternal haemorrhage exist but are not widely available.
8. Note: A negative Kleihauer test does **not** remove the need for Anti-D.
9. If a dose of Anti-D greater than two 600-625 IU vials is required, an intravenous product may be considered. The maximum recommended dose administration rate is 3000 IU 8 hourly to reduce the risk of an adverse reaction arising from rapid clearance of fetal D positive red cells. If an intramuscular dose is used it is recommended that no more than 4 mL is injected at each site.

BACKGROUND INFORMATION ON USE OF ANTI-D IMMUNOGLOBULIN

Reference:

Systematic review of postpartum use and effectiveness of Anti-D

Crowther CA & Middleton P (1997) Anti-Rh-D prophylaxis postpartum, *in* Neilson JP, Crowther CA, et al (eds) *Pregnancy and Childbirth Module of The Cochrane Database of Systematic Reviews. Oxford. Update software (2).*

Immunising dose of fetal red cells

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

Dose of Anti-D Immunoglobulin

1. A dose of 600 - 625 IU will protect against a fetomaternal haemorrhage of 12 ml of blood (6 ml red cells). There is no evidence that a larger dose is more effective for bleeds less than 12 ml of blood (6ml red cells). (*extrapolated from* Pollack W, et al. Transfusion (1971) 31:288-9)
2. Recommendations of the Australian National Health and Medical Research Council state that where a Kleihauer (or other) test indicates that a fetomaternal haemorrhage exceeds 12 ml blood (6ml 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. Recipients who have a moderate or severe thrombocytopenia should not receive intramuscular injections. In this situation, either a product suitable for intravenous administration should be administered intravenously or subcutaneously or an intramuscular product should be given subcutaneously.

Antenatal Sensitising Events

1. Fetomaternal haemorrhage has been demonstrated following the events listed in Indication 1 (refer p1)
2. The Rh D 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. The overall safety for a surviving fetus after antenatal use of Anti-D Immunoglobulin has not been studied in detail. There is no demonstrated evidence of harm from the limited studies performed.
6. Quantified data on risk for Rh D immunisation following the events listed in Indication 1 are incomplete; however the risk may be less than that associated with the birth of an Rh D positive fetus to an Rh D negative woman.
7. It has been common practice in New Zealand and elsewhere to use Rh D Immunoglobulin for the purposes listed in Indication 1 because of the potential risk for fetomaternal haemorrhage.
8. Although no formal evidence exists on the benefit of Anti-D Immunoglobulin after trauma in pregnancy, or for prophylaxis after antepartum haemorrhage, it is common practice to use Anti-D Immunoglobulin for this purpose because of the risk for fetomaternal haemorrhage occurring in these situations.
9. There is a lack of information on the views of women about use of Anti-D Immunoglobulin for these purposes.

Routine use of antenatal Anti-D Immunoglobulin for women who are Rh D negative

Occasional cases of Rh D immunisation are known to occur in late pregnancy. The majority of these cases occur after 28 weeks gestation and most can be prevented by routine antenatal use of Anti-D Immunoglobulin given to all Rh D negative pregnant women who have not previously been immunised to make anti-D.

1. There is considerable lower level evidence but no high level evidence to support the use of routine antepartum Anti-D.
2. Antenatal use of Anti-D Immunoglobulin in Rh D negative women is now an accepted clinical practice in many western countries.
3. Published studies on the safety of antepartum Anti-D Immunoglobulin have evaluated only a limited range of outcome parameters. The studies have not included comprehensive assessment of fetal survival and growth; neonatal morbidity, mortality and immunological status; and long term effects on Rh D negative females exposed to Anti-D Immunoglobulin *in utero* who in adult life are exposed to Rh D positive fetuses.
4. When the dose of Anti-D Immunoglobulin required and appropriate timing for treatment are evaluated the most cost-effective strategy for this treatment is to provide a dose of 600-625 IU at 28 and 34 weeks gestation.
5. On rare occasions a woman may still be accidentally immunised, either before 28 weeks gestation, or despite the use of routine antenatal Anti-D Immunoglobulin prophylaxis. If this occurs, the woman will show the presence of a high or rising titre of anti-D in her plasma. The blood group 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. Routine antibody screening at 34 weeks gestation in women who have received antenatal Anti-D Immunoglobulin at 28 weeks gestation is not now recommended as trace amounts of the 28 week dose of Anti-D Immunoglobulin are likely to be detected.

7. **Where the person managing a pregnancy is concerned over a potential immunising event(s) or the progress of the pregnancy, additional antibody screening will be appropriate and will usually need to be repeated to evaluate changes in antibody titre. NZBS Transfusion Medicine Specialists are available to assist with interpretation of test results.**

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

The clinician should ensure that each Rh D negative woman has accurate information about the risk from anti-D immunisation and its potential consequences, and the benefits and risks from prophylactic use of Anti-D Immunoglobulin. NZBS information leaflets on Anti-D Immunoglobulin and Haemolytic Disease of the Newborn are available.

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

Father is believed to be Rh D negative:

Some Rh D negative women decline to accept Anti-D Immunoglobulin where a test on the father of the fetus/infant has shown an Rh D 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 Rh D 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 Rh D type should normally be performed on two separate samples before it is regarded as confirmed.
3. Confidential steps are taken to check that the man named as father is the father.

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

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

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

Concern is expressed over the safety of the Anti-D Immunoglobulin prophylactic injection

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

1. There is no evidence that the Anti-D Immunoglobulin injection used in NZ has ever spread any important infections, including HIV/AIDS or hepatitis.
2. As the Anti-D Immunoglobulin injection is a blood product it could possibly pass on some infections.
3. NZ blood donors have supplied source plasma for Anti-D Immunoglobulin supplied in NZ. Historically, this supply has been supplemented by either plasma or Anti-D Immunoglobulin from North American donors when local supplies have been insufficient to meet clinical needs. Blood donors in NZ and 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.
4. Blood donations are always tested for the infections: HIV/AIDS, hepatitis B and hepatitis C. Blood donations are only used if there is no evidence of these infections.
5. The process for making Anti-D Immunoglobulin is able to destroy these and many other viruses.
6. There is no evidence that either classical or the variant form of CJD (Creutzfeldt Jakob Disease) has ever been transmitted by manufactured blood products such as Anti-D.

An allergic reaction may occur after injection of blood products, including Anti-D Immunoglobulin, though this is rare. The risk for an allergic reaction is low but will be increased in a person who has previously been pregnant or transfused and lacks a plasma protein antigen present in other individuals.