

USE OF RH(D) IMMUNOGLOBULIN IN UNSENSITISED RHESUS NEGATIVE WOMEN FOR THE PREVENTION OF HAEMOLYTIC DISEASE OF THE NEWBORN

BACKGROUND

Prior to the availability of anti-D immunoglobulin (anti-D Ig), the incidence of Rh(D) alloimmunisation in D negative women following two deliveries of D positive, ABO-compatible infants was approximately 16%, and haemolytic disease of the newborn (HDN) due to anti-D was a significant cause of morbidity and mortality¹. Following routine post-partum administration of anti-D Ig, the rate of alloimmunisation dropped to approximately 2%. A further reduction in the sensitisation rate ranging from 0.17 to 0.28% was achieved by introducing routine antenatal prophylaxis during the third trimester of pregnancy^{2,3,4,5}. Associated with this reduction in sensitisation is a reduction in mortality associated with HDN, from 46/100 000 births to 1.6/100 000 births⁶.

These findings contributed to the National Institute for Clinical Excellence (NICE) recommendation that all Rh(D) negative pregnant women who do not have immune anti-D, should be offered additional routine prophylaxis with anti-D Ig during the third trimester of pregnancy.

OBJECTIVES

The objective of this guideline is to provide practical guidance on the use of anti-D Ig as immunoprophylaxis to prevent sensitisation to the D antigen during pregnancy or at birth for the prevention of HDN.

INDICATIONS FOR ANTI-D PROPHYLAXIS

1. ANTENATAL

Indications for anti-D administration

See Table 1 – Appropriate administration of anti-D Ig, for list of potentially sensitising events according to gestation.

Timing of anti-D Ig administration

Following potentially sensitising events, anti-D Ig should be administered as soon as possible and always within 72 hours of the event. If, exceptionally, this deadline has not been met some protection may be offered if anti-D Ig is given up to 10 days after the sensitising event.

Considerations for raised BMI

The Blood Services/CSL Rh(D) immunoglobulin must be given by deep intramuscular injection. For women with a BMI > 30 particular consideration should be given to factors which may impact on the adequacy of the injection, including the site of administration and the length of the needle used.

No specific additional testing is required because a woman has a BMI > 30. Routine post-administration testing is not required unless there has been a large fetomaternal haemorrhage (FMH); in which case, testing should be in accordance with current established guidelines.¹⁵

PREGNANCIES OF LESS THAN 12 WEEKS OF GESTATION

Anti-D Ig is NOT indicated in most instances – if warranted however, the appropriate dose should be 250 international units. Kleihauer is NOT required.

Gestational age should be confirmed by ultrasound.

Women with anomalous Rh(D) typing results should be treated as D negative until confirmatory testing is completed.

In cases of spontaneous complete miscarriage confirmed by scan where the uterus is not instrumented, or where mild painless vaginal bleeding occurs before 12 weeks, prophylactic anti-D Ig is not necessary because the risk of FMH and hence maternal exposure to the D antigen is negligible.

Evidence that women are sensitised after uterine bleeding in the first 12 weeks of pregnancy, where the fetus is viable and the pregnancy continues, is scant⁷. Therefore anti-D Ig is not necessary in women with threatened miscarriage with a viable fetus where bleeding completely stops before 12 weeks gestation.

However, 250 international units anti-D Immunoglobulin should be administered where bleeding is heavy or repeated, or where there is associated abdominal pain particularly if these events occur as gestation approaches 12 weeks.

Ashburton only stores 625 international units of anti-D. In this circumstance it is reasonable to use 625 international units.

PREGNANCIES BETWEEN 12 WEEKS TO LESS THAN 20 WEEKS OF GESTATION

The appropriate dose of anti-D is 625 international units. Kleihauer is NOT required.

A maternal blood group and antibody screen must be performed to determine or confirm the Rh(D) group and check for the presence of anti-D. If anti-D is identified, further history to be obtained and investigation undertaken to determine whether this is immune (in which case anti-D Ig must not be given) or passive (as a result of previous injection of anti-D Ig). If no clear conclusion can be reached

as to the origin of the anti-D detected, then continue to offer anti-D prophylaxis on the assumption that it may be passive.

For any potentially sensitising event, confirmed Rh(D) negative, previously non-sensitised, women should receive a minimum dose of 625 international units anti-D Ig within 72 hours of the event⁸.

Rh(D) negative women presenting with continual uterine bleeding between 12 and 20 weeks gestation, should receive 625 international units anti-D Ig, at a minimum of 3 weekly intervals, because the half-life of anti-D is 3 weeks.

PREGNANCIES OF 20 WEEKS OF GESTATION TO TERM

The appropriate dose of anti-D is 625 international units. Kleihauer must be requested.

For any potentially sensitising event, Rh(D) negative, previously non-sensitised, women should receive a minimum dose of 625 international units anti-D within 72 hours of the event⁸, regardless of whether the woman has already received anti-D at 28 weeks⁹.

A test for fetomaternal haemorrhage (FMH), ie. Kleihauer ***is required*** as soon as possible following a sensitising event to detect fetal cells in the maternal circulation and, if present, to estimate the volume of FMH to allow calculation of additional anti-D doses required to clear the fetal cells. Additional dose(s) of anti-D Ig should be administered as necessary.

If FMH > 4 mL is detected, follow-up samples are required at 48 hours following an intravenous (IV) dose of anti-D or 72 hours following an intramuscular (IM) dose to check for clearance of fetal cells⁹.

If the two weekly FMH test shows the presence of fetal cells, additional anti-D should be administered to cover the volume of FMH. Blood bank will calculate dose required and details on route of administration.

Each new sensitising event should be managed with an appropriate additional dose of anti-D regardless of the timing or dose of anti-D administered for a previous event.

2. POSTNATAL

In all Rh(D) negative women following birth, ABO and Rh(D) typing should be performed on cord/placental vessel blood and Kleihauer requested. If the baby is confirmed to be Rh(D) positive, women must be recommended to have at least 625 international units of anti-D Ig within 72 hours following birth.

3. INTRAUTERINE FETAL DEATH (IUFD)

In all Rh(D) negative women a Kleihauer should be taken at diagnosis of IUFD.

ABO and Rh(D) typing should be performed on cord/placental vessel blood where possible. If the baby is confirmed to be Rh(D) positive, 625 international units of anti-D is recommended to be given to all Rh(D) negative, previously non-sensitised women.

Where no sample can be obtained from the fetus, an appropriate dose of prophylactic anti-D should be administered as soon as possible within 72h of the diagnosis of IUFD, irrespective of the time of subsequent birth.

ROUTINE ANTENATAL ANTI-D PROPHYLAXIS (RAADP)

CDHB recognises that routine antenatal anti-D prophylaxis for un-sensitised Rh negative women is supported by evidence¹⁰. At this stage CDHB will wait for national guidance on implementation.

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APPENDIX 1 PRINCIPLES, SAFETY AND ADMINISTRATION OF ANTI-D

- Product safety data submitted by manufacturers to inform National Institute of Health and Clinical Excellence technical appraisal guidance¹⁰ indicates a very low rate of reporting a probable or possible adverse event⁶, estimated to be less than one event per 80, 000 doses of anti-D. The majority of reported adverse events were not considered serious. **There is no evidence to suggest that anti-D administered to women during pregnancy is harmful to the fetus.**
- Allergic reactions are very rare but severe hypersensitivity including anaphylaxis may occur. Anti-D preparations may contain trace amounts of IgA (less than 5 µg/mL⁻¹) and hence patients with known antibodies to IgA have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. If symptoms of allergic or early signs of hypersensitivity reactions (including generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) develop, administration of anti-D must be discontinued immediately and appropriate treatment instituted. Medication such as adrenaline should be available for immediate treatment of acute severe hypersensitivity reactions.
- The precise mechanism by which anti-D Ig prevents alloimmunisation is unknown. Possible mechanisms include rapid clearance of anti-D coated D positive red cells by macrophages and down-regulation of antigen-specific B cells^{13,14}.
- The deltoid muscle is an appropriate and safe site for IM administration of anti-D Ig. If the gluteal region is used, particular care should be taken to ensure that the injection is given into muscle, as absorption may be delayed if it only reaches the subcutaneous tissues.
- In women with severe thrombocytopenia (platelet count $\leq 30 \times 10^9/L$) or a history of a bleeding disorder such as severe Von Willebrand disease, anti-D Ig should be administered IV or subcutaneously depending on whether a preparation suitable for IV use is available.
- Antibody screens on maternal pre-transfusion samples may be positive following injection of anti-D Ig. Detectable anti-D may be passive or immune and there is no serological method for distinguishing between the two. Where anti-D is detected in a sample from a pregnant woman, further history should be obtained and investigations undertaken to establish whether this is immune or passive. If no clear conclusion can be reached as to the origin of anti-D, then prophylaxis should continue to be administered in accordance with guidelines for D negative women who have not formed immune anti-D.

TABLE 1 APPROPRIATE ADMINISTRATION OF ANTI-D IMMUNOGLOBULIN

Indication	Dose	Follow-up	Comments
GESTATION: < 12 weeks			
<ul style="list-style-type: none"> PV bleeding with pain Ectopic pregnancy Abdominal trauma Medical/surgical termination of pregnancy 	250 international units IM 625 international units IM in multiple pregnancy	Nil	<ul style="list-style-type: none"> Anti-D required especially if late in 1st trimester (1-12 weeks gestation). For recurrent PV bleeding which settles before the 2nd trimester, one dose of anti-D is sufficient and does not need to be repeated. Not required if uncomplicated spontaneous miscarriage.
GESTATION: 12-20 weeks			
<ul style="list-style-type: none"> Any in utero interventions (amniocentesis, shunts, laser, transfusion, surgery) Abdominal trauma PV bleeding, APH Miscarriage Fetal death, stillbirth 	250 international units IM 625 international units IM in multiple pregnancy	Nil	<ul style="list-style-type: none"> For recurrent PV bleeding, the appropriate dose should be given <u>not less frequently than</u> once every 6 weeks.
GESTATION: > 20 weeks			
<ul style="list-style-type: none"> Any of the indications listed at 12-20 weeks External cephalic version 	625 international units IM 2 x 625 international units (1250 international units) IM in multiple pregnancy	<p>Kleihauer test and Flow cytometry: If Kleihauer is positive, await flow cytometry report for confirmation.</p> <p>Occasional fetal cells is to be interpreted as a very low positive result, covered by 1 vial of Anti-D (625 international units).</p> <p>≤ 5.5 mL = 1 vial of Anti-D (625 international units) > 5.5-11 mL = 2 vials > 11-16.5 mL = 3 vials > 16.5-22 mL = 4 vials</p> <p>Please check the dosage with the haematologist in the event of FMH > 22 mL by flow cytometry</p>	<ul style="list-style-type: none"> For recurrent PV bleeding, the appropriate dose should be given <u>not less frequently than</u> once every 6 weeks. Anti-D as recommended for the sensitizing event should be given <u>irrespective</u> of any planned RAADP. Kleihauer to be collected as baseline before initial anti-D administration and about 30-45 minutes after sensitizing event. Ideally, follow-up Kleihauer to be collected 72h after IM dose (48h after IV).

Indication	Dose	Follow-up	Comments
			<ul style="list-style-type: none"> If repeated doses of anti-D are given because of recurrent PV bleeding, Kleihauer should be repeated every 3 weeks.
POST-PARTUM			
<ul style="list-style-type: none"> If the baby is confirmed to be Rh(D) positive 	625 international units IM 2 x 625 international units (1250 international units) IM if multiple RhD positive births	Kleihauer baseline and ideally follow-up in 72h.	<ul style="list-style-type: none"> Post-partum anti-D is given <u>irrespective</u> of any previous prophylactic anti-D administration.