Trust Guideline on the Management of RhD negative Women in Pregnancy

Document Control:

For Use In:	Maternity Services. Norfolk and Norwich University Hospital Trust		
	All midwifery and gynaecological areas; blood bank; ED		
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Version History:

Version	Date	Author	Reason/Change
V6.0	22/10/2021	Dr Tara Lee	Amendment to 1st trimester
V7.0	15/05/2023	Dr Tara Lee Carol Harvey	- Copying listed PSEs from main text added to flow chart - Separating PSEs and indications from dose of anti-D and FMH testing in main text (appendix 1) - Addition of reporting if 72-hour administration window for anti-D missed. Rhesus is an outdated term, amended to RhD

Previous Titles for this Document:

Previous Title/Amalgamated Titles	Date Revised
None	Not applicable

Distribution Control

Printed copies of this document should be considered out of date. The most up to date version is available from the Trust Intranet.

Consultation

The following were consulted during the development of this document:
Biomedical Scientist i/c of Blood Transfusion
Consultant Obstetrician
Consultant Haematologist

Monitoring and Review of Procedural Document

The document owner is responsible for monitoring and reviewing the effectiveness of this Procedural Document. This review is continuous however as a minimum will be achieved at the point this procedural document requires a review e.g. changes in legislation, findings from incidents or document expiry.

Relationship of this document to other procedural documents

This document is a clinical guideline to Norfolk and Norwich University Hospital Trust (NNUHT) please refer to local Trust's procedural documents for further guidance, as noted in Section 5.

Contents Page

Quick reference : Management pathway for ffDNA for Rh negative women

Quick reference : Management pathway after Potentially Sensitising Event when fetus known Rh positive or fetus unknown Rh status

1. Introduction

1.1. Rationale

Haemolytic disease of the newborn (HDFN) is a condition where fetal or newborn infant's red cells are destroyed by the action of maternal IgG antibodies to antigens present on the fetal red blood cells. The process can begin in intrauterine life and may lead to severe anaemia, *hydrops fetalis* and death *in utero*. In infants, red cell destruction is most severe at birth, but anaemia and jaundice will worsen in the first days of life. If jaundice is severe and not treated by exchange transfusion, the resulting high bilirubin levels may impregnate the basal ganglia, which can lead to death in 70% of affected infants. Surviving infants may have permanent brain damage.

Anti-D is the commonest cause of moderate and severe HDFN and 17% of pregnant women are RhD negative.

The development of anti-D antibodies generally results from feto-maternal haemorrhages (FMH) occurring in RhD negative women who carry RhD positive fetus. The process of sensitisation does not usually affect the initial pregnancy during which it occurs, however, if the mother is exposed to the RhD antigen during a subsequent pregnancy, the immune response is quicker and much greater. Sensitisation depends on the volume of fetal blood entering the mother's circulation and the magnitude of the maternal immune response. Once sensitisation has occurred it is irreversible.

Immunisation can also occur in the absence of an overt sensitising event ("silent bleeds" usually in the third trimester) and hence the National Institute for Health and Care Excellence (NICE) recommends that routine antenatal anti-D prophylaxis (RAADP) should be offered to all RhD negative pregnant women, as postnatal prophylaxis is too late.

1.2. Objective

The objective of the clinical guideline

- To reduce the perinatal mortality and morbidity associated with haemolytic disease of the newborn (HDFN) arising from RhD isoimmunisation.

1.3. Scope

This guideline is intended for use by all staff providing maternity care within Norfolk and Norwich University Hospital Trust.

1.4. Glossary

The following terms and abbreviations have been used within this document:

Term	Definition
A&E	Accident and Emergency Department
HDFN	Haemolytic disease of the newborn
PSE	Potentially sensitising event
Rh D	Previously term Rhesus D now outdated and amended to RhD

NNUHT	Norfolk and Norwich University Hospital Trust
EIA	Equality Impact Assessment
ffDNA	Free fetal DNA
Ig	Immunoglobulins.
FMH	Feto-maternal haemorrhage
NICE	National Institute for Health and Care Excellence
RAADP	Routine antenatal Anti-D prophylaxis
IM	Intramuscular
SHOT	Serious hazards of transfusion
ABO	Classification system for human blood identifying four major blood types. A, B, AB, O
IU	International Units – Measurement of Anti D dosage.
NHSBT	NHS Blood and Transfusion
DCT	Direct Coombes Test
Hb	Haemoglobin
pv	Per vaginal

2. Responsibilities

All staff who provide maternity care at NNUHT should ensure they remain up to date with this guideline

3. Processes to be followed

3.1. Management Pathway for Free Fetal DNA (ffDNA) in Rhesus D Negative Women (<27 weeks)

(See quick reference)
Routine bloods taken at booking for blood group and antibody status.
Take two samples if booking between 24 and 27 weeks.

If RhD negative the woman will receive from the laboratory:

- results letter
- information leaflets
- ffDNA request form

If maternal RhD status known prior to dating scan, ffDNA taken at time of combined screening, if 11+2 weeks gestations or greater.

Sample for ffDNA must NOT be taken before 11+2 weeks gestation by scan.

If maternal RhD status NOT known prior to dating scan, ffDNA taken by CMW (community midwife) at 16 week appointment and completes 28 week anti D request form.

Outcomes:

1. Woman declines ffDNA
    - Routine anti-D prophylaxis at 28 weeks and anti-D prophylaxis following potentially sensitising events.
2. ffDNA result indicates that the fetus is RhD positive or the result uninformative
    - Result letter sent to woman
    - Routine anti-D prophylaxis at 28 weeks and anti-D prophylaxis following potentially sensitising events.
3. ffDNA result indicates that the fetus is RhD negative
    - Result letter sent to woman and NO anti-D prophylaxis given at 28 weeks, NOR following potentially sensitizing events.

For all, maternal and cord bloods sent for blood group testing.
(This will be the case for 12 months following this guideline and will be reviewed thereafter.)

All ffDNA results must be looked up via ICE and careful note taken of the EDD, in order to confirm that the ffDNA result does indeed relate to the current pregnancy. If the results are not available on ICE then the laboratory can be contacted by phone, with the EDD an essential part of the results given verbally, again to ensure the result belongs to the current pregnancy

3.2. What if Anti-D is detectable in samples from pregnant D negative women?

An NHS Blood and Transfusion (NHSBT) report will be generated with the titre of antibody present in maternal blood. Ongoing management will be stated in this report. The likely recommendations are:

- If the anti-D titre is low (<0.1) and can be attributed to **ROUTINE** 28 week anti-D prophylaxis (i.e. **NOT** after any extra anti-D given at any other time after a potentially sensitising event) no further screening or monitoring may be advised apart from a cord blood sample for DCT at delivery, and a neonatal alert does not need to be generated. The result of the DCT should be chased by the midwifery team and if abnormal should prompt notification of the neonatal team. DCT results are usually reported as:
    - No response
    - 1+ / 2 + weak response
    - 3+ / 4 + strong response

Any positive i.e. 1+ or greater should be notified to the neonatal team as soon as they have been reported – usually 1-2 hours after they have been sent.

- If the anti-D titre is low (<0.1) but cannot be attributed to routine anti-D prophylaxis (i.e. antibodies appeared after anti-D given at a potentially sensitising event) then we cannot be sure if the antibodies are from the event or from the prophylaxis. Therefore, more regular group and save samples will need to be sent as per NHSBT report, likely to be every 2 weeks if levels

remain low. If levels remain low a neonatal alert does not need to be done. Cord blood sample for DCT at delivery will need to be done and the result of the DCT should be chased by the midwifery team and if abnormal should prompt notification of the neonatal team (see above).

- If the anti-D titre is high, then more regular blood group and save samples will be required. These will be specified by the identifying NHSBT report. A neonatal alert will be required. If a neonatal alert is in place, i.e., the mother has been assessed and identified as high risk of HDFN, the neonatal team should be alerted when the mother is admitted. When an ARM is performed the neonatal team must be informed so they can get blood on standby for the baby if required as it will need to be irradiated and transferred in Norwich from elsewhere. When she delivers, they can then order the blood if needed. Cord bloods should be sent urgently for Group, DCT, Hb and bilirubin. The midwife looking after the woman should inform the neonatal team that bloods have been sent and results should be chased by the neonatal team.

3.3. When to offer Anti D immunoglobulin?

Pregnant RhD negative women

1. who have declined ffDNA testing
2. where ffDNA testing has indicated a RhD positive fetus
3. where ffDNA testing has been reported as uninformative
4. have not yet had ffDNA testing or results not available (early gestations)

If a patient declines anti-D prophylaxis, the possible implications should be clearly set out. In addition, this should be clearly documented and signed in both the maternity handheld notes and in the buff folder.

3.3.1. Is it safe?

Administration of intramuscular anti-D is best given into the deltoid muscle as injections into the gluteal region often only reach the subcutaneous tissues and absorption may be delayed.

In women with severe thrombocytopenia (platelet count≤30×10^9/L) or a history of a bleeding diathesis such as severe Von Willebrand disease, anti-D Ig should be administered IV or subcutaneously.

There is **no** evidence to suggest that anti-D Ig administered to women during pregnancy is harmful to the fetus.

Immunoglobulins are produced from RhD negative donors who agree to be immunised with RhD positive erythrocytes. Donors are sourced and screened to minimise the risk of blood-borne infections. Serious side effects of anti-D immunoglobulin, such as hypersensitivity reactions, are rare. There is a theoretical risk of infection from as yet undetected blood-born infections.

3.4. Routine Antenatal Anti-D Prophylaxis (RAADP) when fetus known Rh positive or fetus unknown Rh status:

Dose: 1500 iu

It is important that the 28-week sample for blood group and antibody screen is taken **prior** to the first routine prophylactic anti-D Ig injection being given.

Information leaflets should be made available to pregnant women to help with the informed consent process. RhD negative pregnant women who fulfil above criteria should be offered routine antenatal prophylaxis with anti-D Ig (RAADP) with a single dose regimen of anti-D immunoglobulin to be administered between 28-30 weeks gestation.

Routine Antenatal Anti-D Ig Prophylaxis (RAADP) should be regarded as a separate entity and administered in addition to any anti-D Ig that may have been given for a potentially sensitising event, regardless of how recently any extra anti-D has been given.

3.5. Indications for antenatal prophylaxis: potentially sensitising events before delivery when fetus known Rh positive or fetus unknown Rh status

a. **any gestation:**

- Any invasive fetal medicine procedure e.g. amniocentesis, chorionic villus biopsy and cordocentesis, in-utero therapeutic interventions (transfusion, surgery, insertion of shunts, LASER treatment)
- External cephalic version
- Abdominal trauma (sharp/blunt, open/closed)
- Evacuation of molar pregnancy
- **Surgical** management of miscarriage or ectopic pregnancy
- Intrauterine death and stillbirth (see section 3.8)
    - Termination of pregnancy
    - Intraoperative cell salvage (see section 3.8)

b. **≥13 weeks**

- Any antepartum haemorrhage / uterine / PV bleeding (for ongoing vaginal bleeding see section 3.8)
- **Expectant OR medical** management of miscarriage or ectopic pregnancy

3.6. Dose and testing for antenatal prophylaxis following potentially sensitising events before delivery when fetus known Rh positive or fetus unknown Rh status:

Following potentially sensitising events, anti-D Ig should be administered as soon as possible and **must** be given within 72 h of the event. If 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 so should still be given, accepting the effectiveness diminishes with time. For all cases, the dose will be stated as 1500iu. This is because the 250iu dose is no longer made and the supply of the 500iu dose has not been reliable.

If there is a delay in administering anti-D Ig >72 hours after the event, the incident needs to be reported to SHOT (Serious Hazards of Transfusion). The transfusion practitioner team (transfusionpractitionerteam@nnuh.nhs.uk) can be contacted to assist with reporting.

a. **Gestation less than 13 weeks (First Trimester)**
   Dose: 1500iu
   - A test for feto-maternal haemorrhage (FMH) is **NOT** required

b. **Gestation 13 to 20 weeks**
   Dose: 1500iu
   - Assessment of feto-maternal haemorrhage (FMH) is **NOT** required
   - Assessment of maternal blood group and antibody screen should also be performed to confirm RhD group and establish presence of immune anti-D

c. **Gestation 20 weeks to term**
   Dose: 1500iu
   - Assessment of feto-maternal haemorrhage (FMH) **should be performed** to confirm that a sufficient dose of anti-D is administered. This is carried out by haematology on a 6ml EDTA (pink top) bottle.
   - Anti-D should be given as directed by the Haematology laboratory.
   - If FMH >10 mL is detected, follow-up samples are required at 48hrs following an intravenous (IV) dose of anti-D or 72 h following an intramuscular (IM) dose to check for clearance of fetal cells. (1500iu is sufficient to supress immunisation by 10-12ml of RhD positive fetal red cells)
   - Assessment of maternal blood group and antibody screen should also be performed.

3.7. Postpartum Prophylaxis (any form of delivery) when fetus known Rh positive or fetus unknown Rh status:

Dose: 1500iu

Following birth, a cord blood sample should be tested to obtain the ABO and RhD type of the baby. If a cord blood sample is not collected for any reason, a venous sample from the baby should be obtained as soon as possible (contact the neonatal tier 1 doctor – it is the midwives' responsibility to chase this result).
If the baby is confirmed to be RhD positive, the mother should be offered anti-D Ig within 72 h following delivery. Maternal samples for confirmatory ABO and RhD type and FMH testing should be collected after sufficient time has elapsed for any FMH to

be dispersed in the maternal circulation: samples should ideally be taken within 2 hours of delivery. FMH testing should be undertaken to determine if additional doses of anti-D Ig are required.

3.8. Special circumstances when fetus known Rh positive or fetus unknown Rh status:

a) **Ongoing Vaginal Bleeding**
Dose: 1500iu
In the event of continual uterine bleeding which is clinically judged to represent the same sensitising event, with no features suggestive of a new presentation or a significant change in the pattern or severity of bleeding, such as the presence of abdominal pain or another clinical presentation, anti-D Ig should be given at six weekly intervals.

In the event of ongoing intermittent uterine bleeding, estimation of FMH should be carried out at **two weekly** intervals.

b) **Intrauterine Death (IUD)**
Dose: 1500iu
In the event of an intrauterine death (IUD) prophylactic anti-D Ig should be administered within 72 h following the **diagnosis** of IUD, irrespective of the time of subsequent delivery. Maternal samples should be tested for FMH and additional dose(s) given as guided by FMH tests.

c) **Intraoperative cell salvage**
Dose: 1500iu
Where intra-operative cell salvage (ICS) is used during Caesarean section in RhD negative women, where ffDNA has indicated the fetus as RhD positive or was uninformative or fetal blood group is unknown, a minimum dose of 1500iu anti-D Ig should be administered following the re-infusion of salvaged red cells, and a maternal sample should be taken for estimation of FMH 30–45 min after reinfusion in case more anti-D Ig is indicated. It is important that clinicians inform the transfusion laboratory if ICS has been used to ensure that correct dose of anti-D Ig is issued

4. Training & Competencies

All staff who provide maternity care at NNUHT should ensure they remain up to date with this guideline.

5. Related Documents

RCOG Guideline No. 65: Red Cell Antibodies in Pregnancy, The Management of Women with.

BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn

Ectopic pregnancy and miscarriage: diagnosis and initial management - NICE CG154

Routine antenatal anti-D prophylaxis for women who are RhD-negative - NICE TA156

High-throughput non-invasive prenatal testing for fetal RHD genotype - NICE DC25

6. References

1. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn H. Qureshi,1 E. Massey,2 D. Kirwan,3 T. Davies,4 S. Robson,5 J. White,6 J.
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2. National Institute for Clinical Excellence. Routine antenatal anti-D prophylaxis for women who are RhD-negative.
NICE technology appraisal guidance TA156. August 2008.

3. National Institute for Clinical Excellence. Ectopic pregnancy and miscarriage: Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage NG126, April 2019

4. BSH Guideline for blood grouping and red cell antibody testing in pregnancy White. J, Qureshi. H, Massey.E, Needs.M, Byrne.G, Daniels.G, Allard.S Transfusion Medicine 2016 British Blood Transfusion Society

5. Royal College of Obstetricians and Gynaecologists (RCOG) Guideline No. 65: Red Cell Antibodies in Pregnancy, The Management of Women with. May 2014

6. NICE Diagnostic Guidance DG25 High-throughput non-invasive prenatal testing for fetal RHD genotype, November 2016

7. Monitoring Compliance of service to be delivered

Compliance with the process will be monitored through the following:

Key elements	Process for Monitoring	By Whom (Individual / group /committee)	Responsible Governance Committee /dept	Frequency of monitoring
Individual case review of delayed/omitted Anti D administration >72 hours warranting Datix and SHOT report	Review of Datix/SHOT report and review	Maternity Risk and Governance Team and Transfusion Practitioner Team	Maternity Risk and Governance team	Individual case review

The compliance results are to be discussed at maternity risk meetings to review the results and make recommendations for further action. They will also ensure that the actions and recommendations are suitable and sufficient.

8. Equality Impact Assessment (EIA)

Type of function or policy	Existing

Division	Women and Childrens	**Department**	Maternity Services
Name of person completing form	N.Hill	**Date**	18/05/2023

Equality Area	Potential Negative Impact	Impact Positive Impact	Which groups are affected	Full Impact Assessment Required YES/NO
Race	None	None	n/a	No
Pregnancy & Maternity	None		n/a	No
Disability	None	None	n/a	No
Religion and beliefs	Refusal of blood products	None	Jehovah Witness	No
Sex	None	None	n/a	No
Gender reassignment	None	None	n/a	No
Sexual Orientation	None	None	n/a	No
Age	None	None	n/a	No
Marriage & Civil Partnership	None	None	n/a	No
EDS2 – How does this change impact the Equality and Diversity Strategic plan (contact HR or see EDS2 plan)?	No impact			

- **A full assessment will only be required if: The impact is potentially discriminatory under the general equality duty**
- **Any groups of patients/staff/visitors or communities could be potentially disadvantaged by the policy or function/service**
- **The policy or function/service is assessed to be of high significance**

IF IN DOUBT A FULL IMPACT ASSESSMENT FORM IS REQUIRED

The review of the existing policy re-affirms the rights of all groups and clarifies the individual, managerial and organisational responsibilities in line with statutory and best practice guidance.