Use of Non-Invasive Fetal RhD Screening to Determine Fetal RhD Status in RhD Negative Women during Pregnancy - Full Clinical Guideline

Reference no.: UHDB/AN/03:22/A8

Contents

1. Introduction

RhD negative pregnant women carrying a RhD positive fetus are at risk of iso-immunisation which can lead to haemolytic disease of the fetus and newborn. To help prevent this sensitization, women who are RhD negative are recommended to be given Routine Antenatal Anti-D Prophylaxis (RAADP) at 28 weeks gestation and to receive further doses of Anti-D soon after Potentially Sensitizing Events (PSEs), including delivery of the baby. Haematological tests are performed after each PSE at more than 20 weeks gestation to determine the appropriate dose of anti-D. Currently all women whose blood tests show they are RhD negative are given an injection of anti-D immunoglobulin to reduce the risk of potential iso-immunisation.

However, around 40% of RhD negative women will be carrying a fetus that is also RhD negative, meaning that almost half of all the anti-D administered in the antenatal period is unnecessary.

A non-invasive pre-natal test (NIPT) was developed in the 1980s, whereby cell free fetal DNA (cffDNA) which circulates in the maternal circulation could be extracted from a maternal peripheral blood sample. This cell free fetal DNA can then be sequenced to determine if the fetus is RhD negative or RhD positive. This test has originally been undertaken manually and as such was expensive and only used to determine the RhD status of a fetus when maternal anti-D was present. Since 2015, a more automated service has been routinely offered by the International Blood Group Reference Laboratory (IBGRL) which allows all RhD negative pregnant women to be tested to determine the RhD status of the fetus and permit more

individualised management.

The test has been shown to be accurate from 11^{+2}/40 gestation, ideally performed at 16/40 gestation, and should be offered to all RhD negative women if there are no anti-D or anti-G maternal red cell antibodies. If either or both of these red cell antibodies are present, the woman should be referred to the fetal medicine department and the diagnostic test should still be carried out. The diagnostic test looks at more sites on the RhD gene, meaning that D variant genes can be identified, and reports can then be tailored to give recommendations for treating the fetus in that pregnancy as RhD positive or RhD negative.

2. Purpose and Outcomes

- Those women who are carrying a RhD neg baby could avoid unnecessary treatment with anti-D immunoglobulin which is a blood product, and may not need testing following potentially sensitising events or at delivery.
- Those women who are carrying an RhD positive baby can make an informed choice about whether to have treatment with anti-D immunoglobulin. This may lead to better compliance with anti-D immunoglobulin treatment as they will be aware that they are at risk of sensitisation.
- This guideline describes the process to follow for women who choose to access this testing.
- The guideline applies to all women who have been found to be RhD negative on their routine blood group and antibody screen early in pregnancy (<26 weeks) and who are wishing to access UHDB Maternity Services.

3. Key Responsibilities and Duties

- The Blood Bank laboratory staff will identify those pregnant women who are RhD neg and will add a comment to the report alerting midwives to give the option of non-invasive fetal RhD testing or anti-D prophylaxis.
- Midwives have the responsibility to ensure that woman have the chance to discuss non-invasive fetal RhD testing at an antenatal appointment following the initial booking appointment.
- All clinicians have the responsibility to review the woman's blood group in labour and to be aware of the implications of the fetal RhD status.

4. Abbreviations

Anti-D Ig	-	Anti D immunoglobulin
cffDNA	-	cell free fetal DNA
EDD	-	Estimated Date of Delivery
IBGRL	-	International Blood Group Reference Laboratory
LIMS	-	Laboratory Information Management System
MHHR	-	Maternity Hand Held Record
NIPT	-	Non-invasive pre-natal test

PSE	-	Potentially Sensitising Event
RAADP	-	Routine Antenatal Anti-D Prophylaxis

5. Proposed schedule for the management of RhD negative pregnant women

See flowchart for detail (appendix 1)

- All women have booking bloods taken at time of booking
- 16/40 visit with midwife – identify RhD negative women booked at the below Hospitals offering fetal RhD screening and offer non-invasive fetal RhD test.
    - If offer accepted then take pink topped EDTA bottle (6mls)
    - Complete IBGRL request form, obtained from Blood Bank (appendix 2)
        - full patient identifiers on sample and form
        - Full name of hospital: Royal Derby Hospital/Queens Hospital Burton/Nottingham QMC/NUH/Kingsmill/Birmingham: Heartlands/Good Hope.
        - Unique 5 figure NHSBT code:
          Royal Derby: RTGFG
          Burton: RJF02
          Queens Medical Centre/Nottingham City Hospital: RX1RA
          Kingsmill: RK5BC
        - Chesterfield Hospital will be taking this test on women living in Derbyshire area at 20 weeks. Good Hope and Heartlands Hospitals will also be taking this test on women living in the Staffordshire area at 16 weeks. Contact **dhft.pathantenatal@nhs.net** to request the result and patients result to be added to Lorenzo.
        - Stoke/Walsall and Leicester are not yet offering this test so do not offer this test and treat the patient as carrying a RhD positive fetus
        - Estimated date of delivery (EDD) needs to be confirmed by scan
        - All samples to be sent to RDH or Burton irrespective of which Hospital patient booked to deliver at.

- ***SAMPLE MUST NOT TO BE REFRIDGERATED***
- ***Cannot*** be offered to women who already have immune anti-D or anti-G
- ***Cannot*** be offered to women who have a positive antibody screen at booking caused by the remains of anti-D Ig prophylaxis
- ***Can*** be offered to RhD negative women carrying multiple pregnancy
- Rejected samples: offer one repeat only

- Result is reported via Specialist –ICE which is accessed by Blood Bank. Result will then be entered on to the Laboratory Information Management System (LIMS) and transferred to the hospital electronic reporting system (Lorenzo at Derby, Meditech at Burton and the NHSBT IBGRL report attached.
- Results will be added onto the hospital electronic reporting system irrespective of which hospital the patient has booked to deliver at. This result should be recorded within the MHHR
- The report will include the EDD of the pregnancy as well as the predicted fetal RhD genotype
- RAADP offered to RhD negative women who have an inconclusive result or are predicted to be carrying a RhD positive fetus
- RhD negative women who experience a sensitising event to seek medical advice from their booked delivery unit and only have a Kleihauer and Anti-D Ig administered if the fetus is predicted to be Rh positive
- **Late bookers:**
    - If booking >25 weeks gestation but <26+0 weeks, then take an extra 6ml pink topped EDTA sample and if found to be RhD negative then discuss/send for non-invasive fetal RhD testing
    - If booking beyond 26+0 weeks then offer RAADP if RhD negative
- **At delivery:**
    - midwife to take ***cord blood*** from RhD negative women when fetal blood group is predicted to be RhD negative
    - midwife to take ***cord and maternal blood*** from RhD negative women when fetal blood group is predicted to be RhD positive or inconclusive
    - midwife to take ***cord and maternal blood*** from RhD negative women when fetal group is unknown

6. Monitoring Compliance and Effectiveness

As per agreed business unit audit forward programme

7. Associated Policies and References

British Blood Transfusion Society
https://www.bbts.org.uk/blog/noninvasive_prenatal_testing_for_fetal_rhesus-d_status_-_putting_the_/

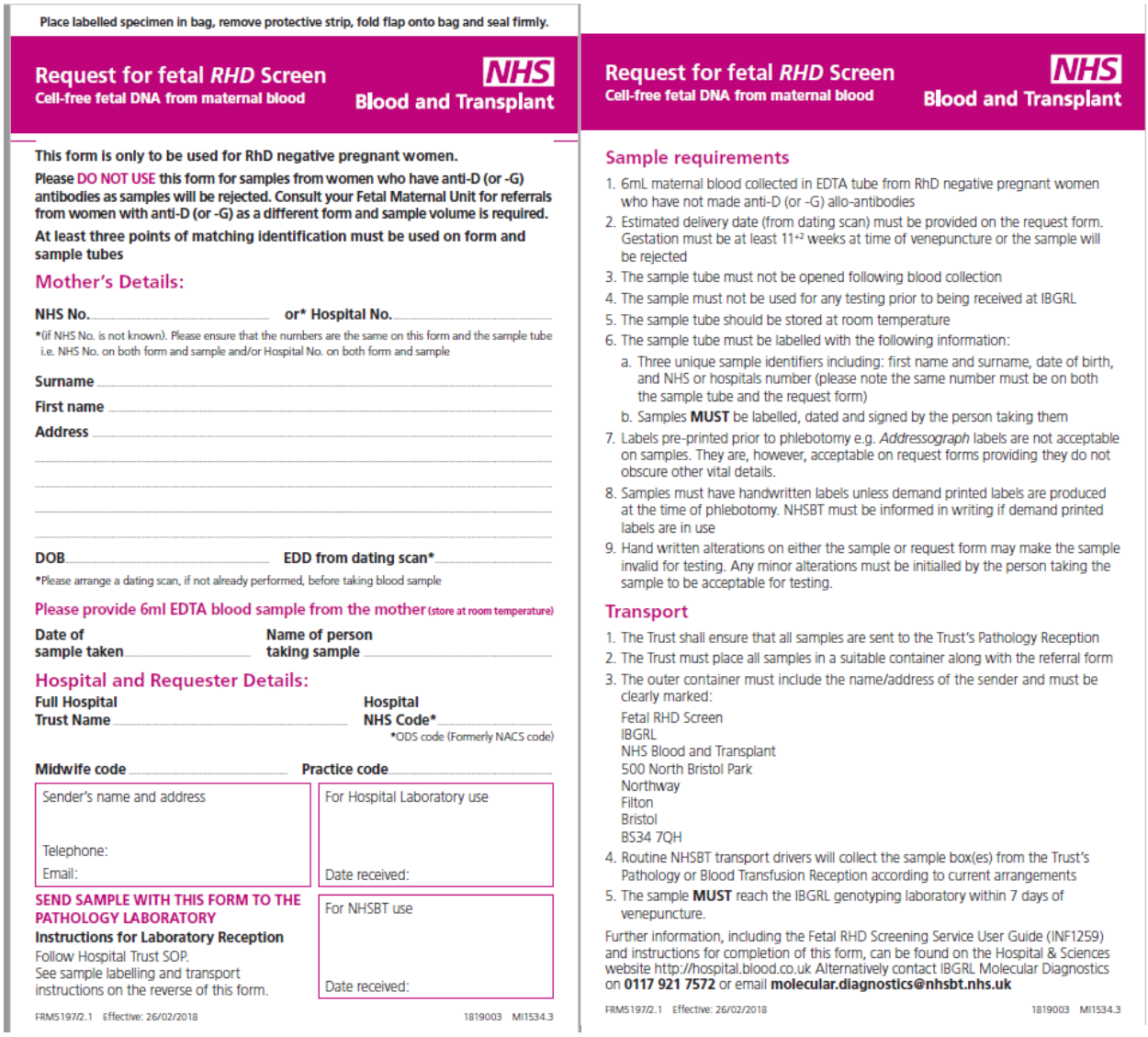
NICE Guideline- High-throughput non-invasive prenatal testing for fetal RHD genotype
https://www.nice.org.uk/guidance/dg25

8. Documentation Control

Reference No: UHDB/AN/03:22/A8	**Version:** **UHDB Version 1**		**Status: FINAL**
Version	Date	Author	Reason
1	Feb 2022	Heather Clarke, Blood Bank Manager, RDH site	New service
Intended Recipients:			
Training and Dissemination: Cascaded electronically through lead sisters/midwives/doctors via NHS.net, Published on Intranet, Article in Business unit newsletter;			
To be read in conjunction with: Anti-D in pregnancy; Antenatal Care, Screening			
Keywords: RhD; Anti-D; NIPT			

Consultation with:	Ms Sundari Devendran, Consultant Obstetrics and Fetal Medicine Community Midwifery seniors team
Business Unit sign off:	Jan 2022: Maternity Guidelines group – Miss S Rajendran 14/02/2022: Maternity Development Committee/ACD – Miss S Raouf 16/02/2022: Maternity Governance Committee – Miss S Dixit (chairing the meeting in February)
Divisional sign off:	22 /02/2022 Divisional Governance
Implementation date:	01/03/2022
Review Date:	Feb 2025
Key Contact:	Cindy Meijer

IBGRL request form (example) Appendix 1



Place labelled specimen in bag, remove protective strip, fold flap onto bag and seal firmly.

Request for fetal *RHD* Screen
Cell-free fetal DNA from maternal blood

NHS Blood and Transplant

This form is only to be used for RhD negative pregnant women.

Please DO NOT USE this form for samples from women who have anti-D (or -G) antibodies as samples will be rejected. Consult your Fetal Maternal Unit for referrals from women with anti-D (or -G) as a different form and sample volume is required.

At least three points of matching identification must be used on form and sample tubes

Mother's Details:

NHS No. ..... **or* Hospital No.** .....

*(if NHS No. is not known). Please ensure that the numbers are the same on this form and the sample tube i.e. NHS No. on both form and sample and/or Hospital No. on both form and sample

Surname .....

First name .....

Address .....

.....

.....

.....

.....

DOB ..... **EDD from dating scan*** .....

*Please arrange a dating scan, if not already performed, before taking blood sample

Please provide 6ml EDTA blood sample from the mother (store at room temperature)

Date of sample taken ..... **Name of person taking sample** .....

Hospital and Requester Details:

Full Hospital Trust Name ..... **Hospital NHS Code*** .....

*ODS code (Formerly NACS code)

Midwife code ..... **Practice code** .....

Sender's name and address Telephone: Email:	For Hospital Laboratory use Date received:
SEND SAMPLE WITH THIS FORM TO THE PATHOLOGY LABORATORY **Instructions for Laboratory Reception** Follow Hospital Trust SOP. See sample labelling and transport instructions on the reverse of this form.	For NHSBT use Date received:

FRM5197/2.1 Effective: 26/02/2018 1819003 MI1534.3

Request for fetal *RHD* Screen
Cell-free fetal DNA from maternal blood

NHS Blood and Transplant

Sample requirements

1. 6mL maternal blood collected in EDTA tube from RhD negative pregnant women who have not made anti-D (or -G) allo-antibodies
2. Estimated delivery date (from dating scan) must be provided on the request form. Gestation must be at least 11^{+2} weeks at time of venepuncture or the sample will be rejected
3. The sample tube must not be opened following blood collection
4. The sample must not be used for any testing prior to being received at IBGRL
5. The sample tube should be stored at room temperature
6. The sample tube must be labelled with the following information:
   a. Three unique sample identifiers including: first name and surname, date of birth, and NHS or hospitals number (please note the same number must be on both the sample tube and the request form)
   b. Samples **MUST** be labelled, dated and signed by the person taking them
7. Labels pre-printed prior to phlebotomy e.g. *Addressograph* labels are not acceptable on samples. They are, however, acceptable on request forms providing they do not obscure other vital details.
8. Samples must have handwritten labels unless demand printed labels are produced at the time of phlebotomy. NHSBT must be informed in writing if demand printed labels are in use
9. Hand written alterations on either the sample or request form may make the sample invalid for testing. Any minor alterations must be initialled by the person taking the sample to be acceptable for testing.

Transport

1. The Trust shall ensure that all samples are sent to the Trust's Pathology Reception
2. The Trust must place all samples in a suitable container along with the referral form
3. The outer container must include the name/address of the sender and must be clearly marked:

   Fetal RHD Screen
   IBGRL
   NHS Blood and Transplant
   500 North Bristol Park
   Northway
   Filton
   Bristol
   BS34 7QH
4. Routine NHSBT transport drivers will collect the sample box(es) from the Trust's Pathology or Blood Transfusion Reception according to current arrangements
5. The sample **MUST** reach the IBGRL genotyping laboratory within 7 days of venepuncture.

Further information, including the Fetal RHD Screening Service User Guide (INF1259) and instructions for completion of this form, can be found on the Hospital & Sciences website http://hospital.blood.co.uk Alternatively contact IBGRL Molecular Diagnostics on **0117 921 7572** or email **molecular.diagnostics@nhsbt.nhs.uk**

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Flowchart of the pathway of care — Appendix 2