NHS National Services Scotland

Pregnant Women with Red Cell Antibodies

Scottish National Clinical Guidance

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PREGNANT WOMEN WITH RED CELL ANTIBODIES

SCOTTISH NATIONAL CLINICAL GUIDANCE

Women with red cell antibodies during pregnancy are at risk of developing Haemolytic disease of the fetus and newborn (HDFN). The aim of this guideline is to outline the management of pregnant women in whom red cell antibodies are identified. The guidance draws on existing UK professional guidelines produced by the British Society of Haematology (BSH) and the Royal College of Obstetricians and Gynaecologists (RCOG) and other relevant literature as cited in the references, towards the end of this document.

Optimal care of pregnant women with red cell antibodies may involve professionals from several disciplines (General Practice, Obstetrics, Midwifery, Neonatology and the Transfusion Laboratory). This guidance is relevant to all members of the multidisciplinary team that may be involved in the care of these women in Scotland.

Timely and accurate communication between all those involved is essential to ensure the best outcome for mother and child. To facilitate communication and documentation, a 'Record of Care' document has been developed in parallel with this guidance.

The production of this guidance has been facilitated by the Scottish National Blood Transfusion Service (SNBTS) Transfusion Team with input from specialists in maternity care and transfusion medicine. A full list of contributors is given at the end of this guidance.

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INTRODUCTION

There are three main reasons for testing for blood group and red cell antibodies during pregnancy:

(1) To establish the mother's blood group and identify any red cell antibodies to ensure that compatible blood for transfusion can be provided for mother and her baby if required.

(2) To identify D negative mothers in order to determine those who should be offered anti-D immunoglobulin (anti-D Ig) prophylaxis.

(3) To ensure early awareness of any red cell antibodies with the potential to result in fetal/neonatal anaemia and/or associated haemolytic disease of the fetus and newborn (HDFN).

The approach to the management of women with red cell antibodies is risk based, depending on an assessment of any history of fetal or neonatal manifestations of HDFN and available diagnostic tools. First affected pregnancies usually (but not always) have clinically minimal HDFN; however subsequent pregnancies may be associated with a worsening degree of fetal anaemia, neonatal anaemia or neonatal jaundice.

Terminology

The nomenclature used for blood group antigens can be confusing, so in this guide the following convention will be used throughout:

- Antigens are named as per their commonly used abbreviation e.g. D, K, Fya
- Antibodies are named using the antigen name and the prefix 'anti' e.g. anti-D
- Genes are given their International Society for Blood Transfusion (ISBT) recommended name e.g. RHD, RHCE, KEL

1. RISK ASSESSMENT

Any woman found, or already known to have red cell antibodies, should be considered as having 'Red' status as per the National Pathways of Maternity Care, and have maternity team (obstetric-led) care. Assessment by an obstetrician with expertise in the management of such women should take place at the earliest possible gestation. Ideally pre-conception counselling should be available for those women with previously identified red cell antibodies who are considering another pregnancy.

The level of risk of HDFN determines the frequency and type of monitoring recommended for the pregnant woman with red cell antibodies. The risk assessment is based on a combination of obstetric history, the type and level of antibody found and the likelihood that the baby has the corresponding antigen. Mothers and babies determined to be at higher risk of HDFN should have antibody levels monitored and fetal scanning performed more frequently to assess the need for antenatal and/or postnatal intervention.

In addition to the obstetric history, it is important to assess the maternal risk for major haemorrhage as suitable blood for maternal transfusion may be difficult to source. If there is an increased likelihood of maternal haemorrhage e.g. placenta praevia, previous postpartum haemorrhage or maternal anaemia, inform your local blood transfusion laboratory and, if required, the relevant SNBTS Regional Blood Transfusion Centre (RTC) as soon as possible (See contact details at end of appendices for further information and contact details).

1.1 Obstetric History

A comprehensive history of all previous pregnancies, whether affected by HDFN or not, should be taken. In particular, previous intra-uterine transfusion (IUT), neonatal anaemia and need for exchange transfusion and/or phototherapy should be noted.

Using suitable discretion and privacy, an attempt should be made to establish whether the father is the same as in any previously affected pregnancy(ies).

If there is a history of a previously affected and/or treated pregnancy, for example where IUT or neonatal treatment were required, the clinical course is often more severe in subsequent pregnancies. Earlier intervention may be appropriate and it is considered good practice to discuss all such cases with the Fetal Medicine Unit (FMU) at the Queen Elizabeth University Hospital in Glasgow at an early stage of pregnancy in order to establish a clear management plan.

1.2 Maternal Antibody Screening

It is recommended (BSH and RCOG guidelines) that **as a minimum**, all women should have a sample taken for ABO group, D type and red cell antibody screening at the time of booking and again at 28 weeks gestation. All samples must be appropriately labelled as per the requirements for transfusion samples to avoid rejection of the sample by the transfusion laboratory and delay in initiating appropriate management.

Red cell antibodies are found in around one percent of pregnancies. Up to 30% of antibodies occur for the first time in the third trimester. Almost every red cell antibody has been implicated in causing some degree of HDFN (See Appendix 2). The commonest cause of clinically significant HDFN is **anti-D**, although the incidence of HDFN due to this antibody is decreasing due to the routine use of anti-D immunoglobulin prophylaxis. However,

sensitisations to the D antigen still occur and reporting of any newly identified cases of immune anti-D to the Serious Hazards of Transfusion (SHOT) programme is encouraged. The hospital transfusion practitioner (TP) will be able to assist with reporting.

The other two main causes of significant HDFN are **anti-c** and **anti-K**, followed by anti-E, anti-Kidd (Jk) and anti-Duffy (Fy) antibodies. Other red cell antibodies can cause HDFN, although this is generally mild (See Appendix 2).

ABO incompatibility between mother and baby is relatively common; however, HDFN as a result of anti-A or anti-B is rare. Haemolysis associated with ABO incompatibility almost exclusively occurs in group O mothers with babies who are type A or type B. Approximately 1% of type O mothers will have a high titre of IgG antibodies against both A and B antigens. The baby is afforded some protection from these antibodies as fetal A and B antigens are not fully developed at birth and non-red cell and secreted A or B substances in the fetus and placenta can neutralise maternal antibody, thereby reducing the amount of circulating IgG available to cause fetal red cell destruction.

If the woman is D negative and has not been sensitised to the D-antigen (i.e. does not have immune anti-D present) she is eligible for anti-D Ig prophylaxis, irrespective of the presence of other red cell antibodies. The sample for antibody screening taken at 28 weeks should be taken **before** the administration of routine anti-D immunoglobulin prophylaxis (RAADP).

If any red cell antibody screening test is positive, further testing is undertaken to identify the antibody specificity and the amount of antibody present. Subsequent investigation and fetal monitoring depends on the type and level of antibody(ies) present.

An increase in antibody level or new red cell antibody formation may alter the timing of follow up for antibody and/or fetal monitoring. The availability of appropriate (antigen negative) blood suitable for transfusion to mother or baby if required should also be considered.

1.3 Maternal Antibody Levels

Higher levels of maternal antibody are associated with an increased risk of HDFN. Antibody levels are expressed as titres e.g. 1 in 4, 1 in 8, 1 in 16 etc. representing doubling dilutions of 'neat' (undiluted) plasma. The reported titre of an antibody is the weakest concentration of plasma at which the antibody can still be detected. Therefore, there is more maternal antibody, and thus more clinical concern, for a titre of 1 in 64 than a titre of 1 in 4. Titres of 1 in 32 or more are usually taken as an indication for antenatal assessment (see section 2.2).

Titres, while useful in monitoring the overall trend in an antibody level, are open to some variation between operators. A semi-automatic technique giving more reproducible results is available for anti-D and anti-c quantification. This test is provided by SNBTS at the West of Scotland Regional Transfusion Centre (WoS RTC) in Glasgow.

Quantification results are obtained by comparison of the mother's sample with an international standard of antibody, and are expressed as international units per millilitre (IU/ml). Correlation between levels of antibody and clinical outcome can be unpredictable at higher levels as the degree of haemolysis is also dependent on other characteristics of the antibody. The level of antibody is therefore only an indication that more direct assessment of the fetus is required. Antibody (D, c) quantification results guiding clinical management are shown in Table 1 below.

Table 1: Antibody quantification (D, c) and risk of HDFN

Level of Risk for HDFN	Antibody Result (IU/ml)	
	Anti-D	Anti-c
Low	0-4	0-7.5
Moderate	4-15	7.5-20
High	**Greater than 15**	**Greater than 20**
British Society for Haematology (2006, 2016)		

1.4 Anti-D Level and Anti-D Prophylaxis

The introduction of prophylactic anti-D Ig to prevent sensitisation of D negative mothers to the D antigen has increased the number of pregnant women in whom anti-D is detected. Passive (prophylactic) and immune anti-D cannot be distinguished serologically; only the disappearance of passive anti-D over time distinguishes its nature from the persistence (and possible rise in level) of immune anti-D.

It has been common practice to infer the nature and/or amount of antibody present on the basis of the reaction strength with reagent cells and any history of administration of anti-D Ig. However, differentiating the likely nature and/or amount of antibody present on the basis of the reaction strength with reagent cells can be unreliable. Concern over the potential to omit anti-D Ig administration in a non-sensitised woman by wrongly assuming that the anti-D present is immune and the failure to follow up sensitised women who are wrongly assumed to have passive anti-D has led BSH and RCOG to suggest that **any** anti-D detected in pregnancy other than at the time of delivery, irrespective of gestational age, history of sensitising event or administration of anti-D prophylaxis, should be referred for **quantification**.

The guidelines go on to suggest that the appropriate management strategy for women with anti-D can then be defined on the basis of the quantification result. Anti-D levels of less than 0.2 IU/ml are regarded as passive, do not need serial monitoring, and anti-D Ig prophylaxis is continued. Levels between 0.2 and 0.4 IU/ml are likely passive **but follow up as if sensitisation has occurred while continuing to offer prophylaxis** until the nature of the antibody is confirmed by its persistence or otherwise over time is recommended.

Scottish data suggests that the recommendation to quantify anti-D in all samples where it is detected has the potential to significantly increase the costs of antenatal testing. In advance of the publication of proposed unifying RCOG/BSH/Scottish guidelines, no change to current Scottish practice in regard to quantification of anti-D is made here. However, the key point for clinical practice is to ensure that **women found to have anti-D present should be reviewed more frequently for antibody screening while continuing to offer prophylaxis until the nature of the antibody is confirmed by its persistence or otherwise over time.**

1.5 Paternal Testing

As blood groups are heritable characteristics, knowledge of the father's blood group can assist in determining whether the baby is at risk of HDFN as a consequence of any maternal antibody that is identified. Paternal blood group and red cell phenotype should be determined where possible when antibodies that are associated with a risk of HDFN are present.

Confidential counselling should be used to establish that the woman is certain of the paternity of this baby, and if the father would be available and willing to provide a blood sample to ascertain the likely blood group of the baby for the purposes of risk assessment. If paternal phenotyping and/or cell free fetal DNA testing (see section 1.6) is not possible, care should

be provided as if the baby is antigen positive and therefore at risk of HDFN from the antibody to that antigen.

The process for requesting paternal testing will vary locally. Check with the local laboratory before taking the sample. The request form accompanying such samples must clearly indicate in the clinical details section the origin of the sample, the relationship to the woman with antibodies and the woman's name, date of birth and CHI or hospital number in the 'clinical details' part of the request form.

If the paternal phenotype indicates that the father is antigen negative:
The baby cannot have the antigen of interest and therefore cannot be affected by maternal antibody to that antigen. Care for this pregnancy should continue as for a non-sensitised pregnancy. If an antibody of a different specificity develops at a later date, further risk assessment and care should be initiated as per this guidance.

If the paternal phenotype indicates that the father expresses the antigen of interest:
The baby may, or may not, carry the relevant antigen(s); cell free fetal DNA testing may be used, if available, to predict whether the baby has the antigen(s) of interest. This testing is no longer carried out in Scotland and can be arranged by direct communication with the NHSBT Red Cell Immunohaematology laboratories in Filton (see section 1.6).

Paternal zygosity testing is no longer available in Scotland. This service is available from the NHSBT RCI laboratories and, as for cell free fetal DNA analysis, testing can be arranged by contacting their laboratory directly (see section 1.6 for contact information). This may be indicated where cell free fetal DNA testing is not currently available for the antigen of interest.

Despite confidential counselling, the issue of false paternity remains a possibility, therefore any unexpected new antibody or change in antibody level should trigger monitoring (as per section 2.1).

1.6 Cell Free Fetal DNA Testing

It is now possible to analyse cell free fetal DNA (cffDNA) that is present in maternal plasma using polymerase chain reaction (PCR) techniques. The analysis is restricted to prediction of fetal red cell antigen status for D, C, c, E and K. A maternal sample for cell free fetal DNA testing may be considered if the paternal phenotype indicates that the father is heterozygous for any of these antigens (or the phenotype is unknown), and the mother has antibody to D, K, C, c, or E. Testing to predict the presence of other fetal red cell antigens is not currently available.

This service is no longer available in Scotland. All details relating to this service, including contacts for enquiries (Tel: 0117 921 7572, email: molecular.diagnostics@nhsbt.nhs.uk), sample requirements, request forms, the address for samples and arrangements for invoicing can be found under Molecular Diagnostics on the IBGRL website https://ibgrl.blood.co.uk/services/user-guides/.

The amount of fetal cell free DNA shed into the maternal circulation increases throughout pregnancy; however, there is considerable individual variation in the levels of cell free fetal DNA present. Therefore, if a result is either inconclusive or negative for the allele of interest with no confirmation of the presence of cffDNA, a repeat sample will be requested in 2-4 weeks. As cffDNA detection of RHc and KEL are technically difficult assays, all negative results for these alleles will routinely generate a request for a repeat sample in 2-4 weeks.

The acceptable gestation times for testing are:
RHD, RHC , RHE and RHc: > 16 weeks gestation
KEL > 20 weeks gestation. Repeat at 28 weeks if negative.

Please see website for sample and transport details:
https://ibgrl.blood.co.uk/services/molecular-diagnostics

If cell free fetal DNA testing suggests that the baby is antigen negative:
The baby is not likely to be at risk from this antibody. It is important to remember that occasional false negative results have been reported (<1%) using cell free fetal DNA testing. Therefore, it is recommended that if subsequent antibody testing suggests a rising antibody level, the possibility that the fetus may in fact be antigen positive should be considered and the pregnancy should be monitored as per the flow chart (Appendix 1).

If cell free fetal DNA testing suggests that the baby is antigen positive:
The baby is 'likely to be at risk' of HDFN, and care should be as per flow chart (Appendix 1) and this guidance.

2. MONITORING OF THE PREGNANCY AT RISK OF HDFN

2.1 Antibody Monitoring

Red cell antigens are expressed on fetal red cells from around 38 days gestation.

Sensitisation of women to antigens carried by their babies occurs as a result of feto-maternal haemorrhage (FMH). This occurs in 75% of all pregnancies with the incidence and degree of FMH increasing with gestational age. The highest risk of FMH is at delivery accounting for the observation that sensitisation often affects subsequent pregnancies more severely.

Once sensitised, continued exposure to fetal red cell antigens stimulates further antibody production and a rise in the maternal antibody level; thus the recommended frequency of antibody testing increases as the pregnancy advances. Antibodies that arise for the first time in the third trimester are less likely to cause significant HDFN.

Anti-D, anti-c or anti-K antibodies
Once detected, these antibodies, as the most commonly associated with significant HDFN, should be monitored monthly until 28 weeks and then fortnightly until delivery. If the antibody level is in the moderate or high risk range (see Table 1, Section 1.3), referral for fetal assessment is recommended (see section 2.2).

NB: In addition to causing haemolysis, Anti-K antibody can also bind to red cell precursors in the bone marrow, reducing fetal erythropoiesis through inhibition or immune destruction, and contributing to fetal anaemia. Historically, titres of Anti-K did not correlate well with the risk of HDFN and significant fetal anaemia could arise in the presence of low levels of Anti-K antibody. However, more recent data suggests that severe HDFN due to anti-K is unlikely at titres less than 1/32. However, BSH and RCOG guidelines recommend that, unless the father is known to be K negative, fetal assessment is undertaken when Anti-K is first detected.

Other Rh (C, E, e), Duffy, and Kidd antibodies
These antibodies are considered as having a lower risk of producing significant HDFN. If present at booking at a titre of less than 1/32, in the absence of a history of a previously affected pregnancy, repeat testing at 28 weeks is recommended. Women with these antibodies at a titre of 1 in 32 or more, and/or a history of a previously affected pregnancy should be considered as a moderate risk and should have the antibody monitored monthly until 28 weeks and then fortnightly until delivery; referral for fetal assessment is also recommended (see section 2.2).

Antibodies of other specificity
Other antibodies are considered as low risk for HDFN unless there is a history of a previously affected pregnancy; routine testing at booking and again at 28 weeks is sufficient.

2.2 Fetal Assessment

Ultrasound and middle cerebral artery peak systolic velocity (MCA PSV) doppler scanning are used to look for signs of fetal anaemia. Scanning should be performed by a suitably trained person and the result interpreted by a clinician with expertise in the management of HDFN. Referral to the FMU in Glasgow is indicated if at any stage there are ultrasonographic features suggestive of anaemia (e.g. ascites, pleural effusions, hydrops, placentomeagly).

MCA Doppler scanning is not usually indicated if maternal antibodies are present at levels associated with low risk of HDFN (Table 1). Where an antibody level, whether measured by titre or by quantification, indicates moderate risk of HDFN, and gestation has reached 18 weeks, clinicians should consider further investigation/assessment of the baby using MCA PSV Doppler scanning. MCA peak systolic velocities of greater than 1.5 multiples of the median (MoM) have good predictive value for moderate to severe anaemia (see Appendix 3). As anaemia can develop rapidly, regular monitoring, at least fortnightly, is suggested.

Unless the baby is known to be antigen negative, when an antibody level suggests a 'high risk' for HDFN, MCA PSV Doppler scanning should be undertaken as soon as is practical in order to determine the presence and severity of any fetal anaemia. If antibody levels exceed the high risk thresholds at less than 18 weeks gestation, then referral to the FMU in Glasgow is indicated.

MCA PSV Doppler Scanning is less sensitive for prediction of fetal anaemia beyond 35 weeks gestation. Decisions regarding timing of delivery should also take into account the obstetric history, antibody level and MCA PSV trend. If in doubt, please discuss with the FMU in Glasgow and neonatology.

MCA PSV Doppler Scanning is indicated if:

- Anti-D antibody quantification continues to rise above 4 IU/ml
- Anti-c antibody quantification continues to rise above 7.5 IU/ml
- Anti-K antibody is present
- Any other antibody is present at a titre $\geq$ 1 in 32
- There is history of previously affected/treated pregnancy

Discussion with the FMU in Glasgow is indicated if:

- MCA PSV exceeds 1.5 MoM
- Antibody levels exceed the thresholds stated at less than 18 weeks gestation
- MCA PSV is in normal range, but there are ultrasonographic features suggestive of anaemia (e.g. ascites, pleural effusions, hydrops, placentomegaly)
- MCA PSV is not available locally

Once serial MCA dopplers are being performed, the value of further titration / quantification of antibody is doubtful, however, samples should still be screened for the presence of any additional antibodies as further antibodies may impact on the provision of suitable blood for mother and baby.

3. FETAL MEDICINE UNIT ASSESSMENT

The FMU located in the Queen Elizabeth University Hospital in Glasgow is the only unit in Scotland where intra-uterine transfusion (IUT) can be performed. IUT is a highly specialised technique that aims to maintain the fetal haemoglobin at a level sufficient to prevent the adverse effects of anaemia and ultimately the development of hydrops. Any woman at risk of requiring an IUT should be discussed with FMU clinicians.

3.1 Referral to the FMU in Glasgow

Individual cases should be discussed with the FMU in Glasgow if:

- The fetus is known to be at high risk of HDFN (through paternal and/or genetic testing)
- There is a history of a previously affected / treated pregnancy
- There is an antibody level suggestive of moderate or high risk of HDFN and MCA PSV is not available at referring maternity unit
- There is a MCA Doppler PSV exceeding 1.5x MoM
- There is ultrasound evidence of fetal anaemia

The discussion will determine whether it is appropriate for the woman to attend the FMU in Glasgow or to continue attending the referring maternity unit with an agreed plan of care. If in doubt, please call the FMU in Glasgow to discuss individual cases.

3.2 Intra-Uterine Transfusion

On referral to the FMU in Glasgow women will be assessed and IUT offered if appropriate.

If IUT is being considered the transfusion laboratory at the Queen Elizabeth University Hospital and the SNBTS WoS RTC should be informed as soon as possible to allow them to source and make available suitable blood for transfusion. Please note that blood for IUT has a high specification and may require some time to organise, especially if rare blood types are involved as donors may need to be called specifically (see Appendix 4 for the specification of blood components for IUT).

Several transfusions may be required to maintain an adequate fetal haemoglobin level while the pregnancy advances to a gestational age that will ensure the survival of the neonate. The FMU in Glasgow will liaise with the relevant referring maternity unit to schedule delivery generally 7-10 days following the last IUT at a unit with neonatal intensive care facilities.

After 26 weeks gestation, steroids are usually given prior to IUT due to the increased risk of premature delivery. The need for steroids should be discussed at time of referral.

IUT is not usually initiated after 34 weeks gestation. If there is a sudden and significant rise in antibody level after this gestation, discuss individual care and potential delivery with the FMU in Glasgow.

If an IUT is performed, it is important that the clinical team and the blood bank at any other hospital that may be involved in the subsequent care of the woman and her baby is informed of this occurrence. Any neonate who has received an IUT will require **irradiated blood for**

exchange or top up transfusion following delivery. This requirement must be recognised and specifically requested by those providing care for the neonate. The referring Obstetrician should inform their local blood bank prior to delivery for any woman who has received and IUT so that the requirement for irradiated blood for the neonate can be highlighted at the time of delivery.

Once a woman has started into an IUT programme there is no benefit in continuing to monitor antibody levels, however, samples should still be screened to ensure detection of any additional antibody specificity that may impact on the provision of suitable blood for the baby and mother.

4. DELIVERY

4.1 Delivery Plan

The delivery plan within the record of care should be completed as soon as is practical. Delivery would normally be spontaneous or by induction of labour if there are no contraindications. There is usually no additional need for elective caesarean section. The delivery should take place in a location with facilities for neonatal intensive care. The neonatal team should also be involved in drawing up the delivery plan.

Women who have received IUT:
Delivery is arranged 7 to 10 days after the last IUT at a unit with neonatal intensive care facilities, following discussion with the FMU in Glasgow.

Baby at moderate or high risk, but MCA PSV less than 1.5x MoM:
Deliver by 37 weeks.

Women with previous significant HDFN, but with MCA PSV less than 1.5x MoM:
Discuss with the FMU in Glasgow and deliver by 37 weeks.

Women with anti-K <1 in 8, anti-D <4 IU/ml or anti-c <7.5 IU/ml:
Deliver by 40 weeks.

All other women:
Await the spontaneous onset of labour

If induction or operative delivery is planned the relevant local transfusion laboratory, at the location where this will take place, should be informed as soon as the date is confirmed. This will ensure timely provision of suitable blood for maternal and / or neonatal transfusion. Any increased likelihood of maternal transfusion (e.g. existing maternal anaemia or increased risk of obstetric haemorrhage) should also be noted at the same time.

4.2 Admission in Labour or for Delivery

Check the delivery plan within the record of care for any other specific instructions regarding delivery. The Obstetric Team, Neonatal Team/Unit and the local hospital blood bank should all be informed of admission for delivery or potential delivery.

A maternal group and screen sample should be sent immediately on admission for delivery or if there is potential for delivery, to allow blood bank to screen for the presence of any further antibody. Assessment of antibody levels is not required at this time.

4.3 Delivery

A paediatrician should assess the newborn and in some cases it will be appropriate for the paediatrician to be present at delivery. The attending paediatrician should document planned neonatal observation and management.

Cord blood should be taken for full blood count (FBC), ABO and D group, direct antiglobulin test (DAT), red cell eluate and serum bilirubin. The cord cells can also be tested for the presence of the relevant antigen when antibody other than anti-D is present.

Irrespective of the presence of other red cell antibodies, all D negative women who have not been sensitised to the D antigen should have a sample sent for a Kleihauer test to estimate the degree of FMH at delivery. The sample should be taken at least 45 minutes after placental separation to allow distribution of fetal cells in maternal circulation. If the baby is D positive anti-D immunoglobulin should be given in sufficient dose to cover the reported volume of FMH in line with established practice.

4.4 Post Delivery

The newborn infant may require phototherapy, top up transfusion or exchange transfusion depending on the degree of haemolysis and/or anaemia present. Neonates who have required IUT will have suppressed erythropoiesis and are likely to require top up transfusion and on occasions require erythropoeitin treatment. Blood for exchange or top up transfusion ***must be irradiated if there has been a prior IUT.***

Babies born to women with red cell antibodies may be at risk of severe hyperbilirubinaemia in the neonatal period, even where there were no signs of fetal complications during pregnancy. Liaison between obstetric and neonatal teams should take place around time of delivery and during the neonatal period.

The woman should be counselled regarding the risks for future pregnancies. The need for early assessment and ideally pre-natal counselling should be emphasised.

5. COMMUNICATION AND DOCUMENTATION

5.1 Pregnant Women with Red Cell Antibodies – Record of Care

The record of care accompanying this guidance was developed to complement the original hand held maternity record. In the absence of an electronic equivalent, this paper record may continue to be used if desired. The record should be commenced as soon as is practical after the discovery of red cell antibodies. All relevant care, investigations and treatment should be documented in the record. The record should be held by the woman and brought to each appointment or assessment.

The delivery plan within the record of care should be completed as soon as is practical. The attending paediatrician should document observations and planned neonatal management on the delivery plan following initial assessment of the newborn.

The outcome form should be completed as soon as is practical. The information collected may be used for auditing and to monitor trends in incidence and outcomes of pregnancies where red cell antibodies are present.

It is suggested that a distribution list is created at the time of booking to enable prompt and inclusive communication regarding the care of women with red cell antibodies. This can be used to share relevant results of investigations and management plans between the members of the multidisciplinary team providing care. This list should include as an initial minimum the GP, midwife, obstetrician, paediatrician, and laboratory manager involved in the care of the woman. If a referral is made to a specialist obstetric unit, the names of the obstetrician, midwife and laboratory manager involved at that institution should be added to the list. If the woman is referred to the FMU in Glasgow, the name of the obstetrician, midwife and laboratory manager at the Queen Elizabeth University Hospital in Glasgow should be added. If at any time samples are sent to the WoS RTC or the NE Scotland RTC in Aberdeen, the name of the relevant laboratory manager should be added.

5.2 The Pregnant Woman

The pregnant woman should be fully involved in all decisions regarding her care and treatment. She should be made aware of the significance of her handheld record of care, particularly when care is provided by two or more maternity units.

5.3 Blood Transfusion Laboratory

In common with the clinical services involved with the care of women with red cell antibodies, a number of blood transfusion laboratories in different locations may be involved in the care pathway.

<u>Local Blood Transfusion Laboratory:</u>
This is the hospital transfusion laboratory or blood bank at the booking maternity unit. This may also be one of the SNBTS regional transfusion laboratories.

SNBTS Regional Blood Transfusion Laboratories:

Region	National Services
East of Scotland Blood Transfusion Centre, Dundee	Antibody titration
North of Scotland Blood Transfusion Centre, Inverness	Antibody titration
NE Scotland Blood Transfusion Centre, Aberdeen	Antibody titration
SE Scotland Blood Transfusion Centre, Edinburgh	Antibody titration
West of Scotland Blood Transfusion Centre, Glasgow	Antibody quantification Blood for IUT (irradiated at JCC beforehand)

The hospital blood transfusion laboratories, in collaboration with SNBTS, will provide blood suitable for maternal, intra-uterine and/or neonatal transfusion as required. It is vital to ensure that the relevant transfusion laboratory where the episode of care is taking place is aware of the presence of the woman in their service area. **Please inform the relevant local transfusion laboratory when:**

- A decision is made to transfuse (maternal, IUT, neonatal top-up or exchange), or if transfusion is likely
- A decision is made on place and date of delivery
- Mother and/or neonate are transferred between maternity units
- This pregnancy ends in miscarriage, termination of pregnancy or stillbirth/intrauterine death. This is particularly important if arrangements have been made to call donors for anticipated transfusion needs and these are no longer required.

Samples for blood grouping and antibody screen should be sent to the blood transfusion laboratory that usually processes samples for the clinical unit where the sample is taken. Any samples showing irregular antibodies will be forwarded by that laboratory to the appropriate regional blood transfusion laboratory for further testing. The regional laboratory will forward any samples that require antibody quantification to the WoS RTC Laboratory in Glasgow. Reporting of test results will be cascaded back through the sequence of laboratories in the same manner.

Blood for IUT will be sourced and cross matched by the WoS RTC in Glasgow before being despatched to the blood bank at the Queen Elizabeth University Hospital, Glasgow for subsequent issue to the patient. Please provide sufficient notice when ordering product to allow time for the unit to be freshly irradiated at the JCC in Edinburgh before being sent to Glasgow for cross-matching.

5.4 Neonatal Team

Liaise with the neonatal team who will care for the baby, and involve them in the discussion of the delivery plan. The paediatrician who assesses the newborn should document a plan of care.

5.5 FMU in Glasgow

The specialist team at the FMU in Glasgow are available to provide advice at any time. Please call to discuss general or specific queries.

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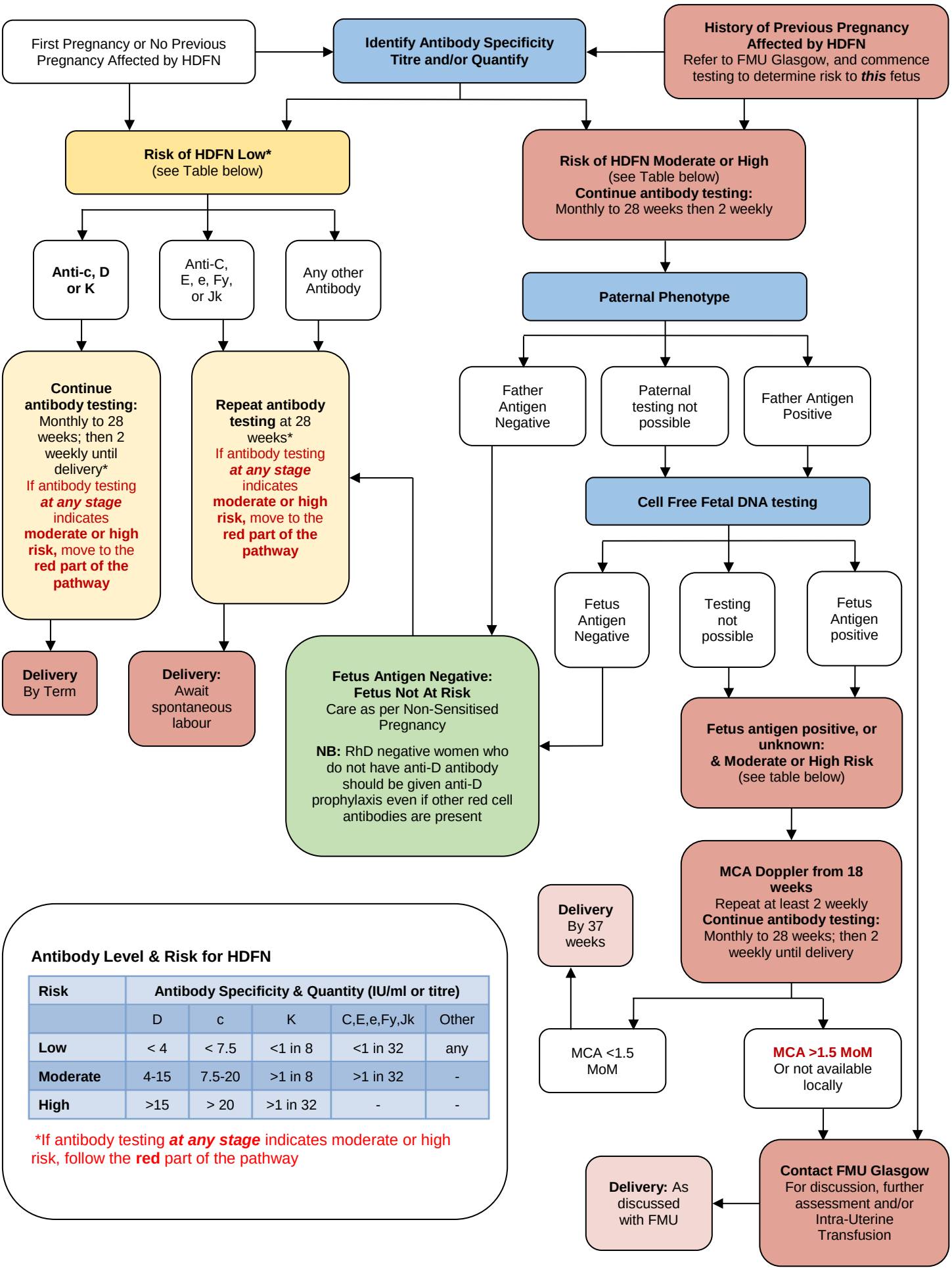
APPENDICES

Appendix 1: Flow Chart Summarising Clinical Care for Pregnant Women with Red Cell Antibodies



Antibody Level & Risk for HDFN

Risk	Antibody Specificity & Quantity (IU/ml or titre)				
	D	c	K	C,E,e,Fy,Jk	Other
Low	< 4	< 7.5	<1 in 8	<1 in 32	any
Moderate	4-15	7.5-20	>1 in 8	>1 in 32	-
High	>15	> 20	>1 in 32	-	-

*If antibody testing ***at any stage*** indicates moderate or high risk, follow the **red** part of the pathway

Appendix 2: Red Cell Antibodies and Risk of HDFN

Antibodies Frequently Associated with Severe Disease	
Antigen System	**Specific Antigen**
Kell	-K (K1)
Rh	-c, D
Antibodies Infrequently Associated with Severe Disease	
Antigen System	**Specific Antigen**
Colton	-Co^{a} -Co3
Diego	-ELO, -Di^{a}, -Di^{b}, -Wr^{a}, -Wr^{b}
Duffy	-Fy^{a}
Kell	-Js^{b}, -k (k2), -Kp^{a}, -Kp^{b}, -K11, -K22, -Ku, -U1^{a}
Kidd	-Jk^{a}
MNS	-En^{a}, -Far, -Hil, -Hut, -M, -Mi^{a}, -Mt^{a}, -MUT, -Mur, -M^{v}, -s, -s^{D}, -S, -U, -Vw
Rh	-Be^{a}, -C, -Ce, -C^{w}, -ce, -E, -E^{w}, -Evans, -G, -Go^{a}, -Hr, -Hr$_{o}$, -JAL, -Rh32, -Rh42, -Rh46, -STEM, -Tar
Scianna	-Sc2, -Rd
Other	-Bi, -Good, -Heibel, -HJK, -Ht^{a}, -Jones, -Joslin, -Kg, -Kuhn, -Li^{a}, -MAM, -Niemetz, -REIT, -Reiter, -Rd, -Sharp, -Vel, -Zd
Antibodies Associated with Mild Disease	
Antigen System	**Specific Antigen**
Duffy	-Fy^{b}, -Fy^{3}
Gerbich	-Ge^{2}, -Ge^{3}, -Ge^{4}, -Ls^{a}
Kell	-Js^{a}
Kidd	-Jk^{b}, -Jk^{3}
MNS	-Mit
Rh	-C^{x}, -D^{w}, -e, -HOFM, -LOCR, -Riv, -RH29
Other	-At^{a}, -JFV, -Jr^{a}, -Lan
Moise KJ (2005), Red Blood Cell Alloimmunisation in Pregnancy, Seminars in Haematology	

Appendix 3: Reference Range of Fetal Middle Cerebral Artery Peak Systolic Velocity

Reference range of fetal middle cerebral artery peak systolic velocity (MCA-PSV) median and 1.5 multiples of the median (MoM) values during pregnancy

GA (weeks)	MCA-PSV (cm/s)	
	Median	1.5 MoM
14	19.3	28.9
15	20.2	30.3
16	21.1	31.7
17	22.1	33.2
18	23.2	34.8
19	24.3	36.5
20	25.5	38.2
21	26.7	40.0
22	27.9	41.9
23	29.3	43.9
24	30.7	46.0
25	32.1	48.2
26	33.6	50.4
27	35.2	52.8
28	36.9	55.4
29	38.7	58.0
30	40.5	60.7
31	42.4	63.6
32	44.4	66.6
33	46.5	69.8
34	48.7	73.1
35	51.1	76.6
36	53.5	80.2
37	56.0	84.0
38	58.7	88.0
39	61.5	92.2
40	64.4	96.6

GA, gestational age. (Modified from G Mari *et al.* *N Engl J Med* 2000; **342**: 9-14[1],)

Appendix 4: Specification of Blood Components for IUT

- Donation must be from an accredited donor
- Group O or ABO identical with the fetus, and D negative in most cases
- Negative for the relevant antigen(s) determined by maternal antibody status and IAT crossmatch compatible with maternal serum
- K negative
- In CPD, not SAG-M
- Used within 5 days of collection
- Free from clinically significant antibodies including high-titre anti-A and anti-B
- CMV antibody negative
- Gamma irradiated and used within 24 hours of irradiation
- Leucocyte depleted
- Haematocrit of > 0.7

LIST OF ABBREVIATIONS

ABO	ABO notation for the ABO blood group system
cffDNA	Cell-free fetal DNA
CHI	Community Health Index
CMV	Cytomegalovirus
CPD	Citrate phosphate dextrose
D C c E e	Antigens of the Rh blood group system
DAT	Direct antiglobulin test
DNA	Deoxyribonuecleic acid
FBC	Full blood count
FMH	Fetomaternal haemorrhage
FMU	Fetal Medicine Unit
HDFN	Haemolytic disease of the fetus & newborn
IAT	Indirect antiglobulin test
ISBT	International Society for Blood Transfusion
IU	International units
IUD	Intra-uterine death
IUT	Intra-uterine transfusion
K	K1 antigen of the Kell blood group system
MCA	Middle cerebral artery
ml	Millilitre
MoM	Multiples of median
NE	North East
MCA PSV	Middle cerebral artery peak systolic velocity
PCR	Polymerase chain reaction
RTC	Regional Transfusion Centre
RhD	D antigen of the Rh blood group system
SAG-M	Saline adenine glucose mannitol
SE	South East
SHOT	Serious Hazards of Transfusion
SNBTS	Scottish National Blood Transfusion Service
SNBTS TT	SNBTS Transfusion Team (previously Better Blood Trasnsfusion)
TP	Transfusion Practitioner
WoS	West of Scotland

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