Worcestershire Acute Hospitals NHS Trust

Pregnant Women with Red Cell Antibodies

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Key Amendments

Date	Amendments	Approved by

Red Cell Antibodies

Introduction

Approximately 1% of pregnant women are found to have clinically significant red cell antibodies which can lead to haemolytic disease of the fetus and newborn (HDFN). Anti-D, anti-c and anti-Kell (K) are the antibodies most likely to cause HDFN although in the case of anti-c this may be delayed. Other antibodies, particularly anti-E, anti-Duffy, anti-M and anti-S, have a lower risk of causing fetal anaemia but may result in severe neonatal hyperbilirubinaemia.

Any woman found, or already known to have red cell antibodies, should be referred for consultant led antenatal care in pregnancy.

The aim of this guideline is to outline best practice in the management of pregnant women in whom red cell antibodies are identified.

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

1. To ensure prior knowledge of blood group and identify any red cell antibodies that may make the cross-matching of blood for transfusion difficult.
2. To identify Rh D negative mothers in order to determine those who require anti-D prophylaxis.
3. To ensure early awareness of any red cell antibodies that have the potential to result in fetal/neonatal anaemia and/or associated Haemolytic Disease

* For the purposes of this guidance, the term ‘HDFN’ is used throughout, although in the context of an

Risk Assessment

1. Comprehensive History

A comprehensive history of all previous pregnancies, whether affected 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, attempt to establish whether the father of this pregnancy is the same as that of any previously affected pregnancy (ies).

If there is 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. Early intervention may be appropriate and these case need referral to local fetal medicine clinic and referral to West Midland Fetal Medicine Centre (WMFMC) at an early stage of pregnancy in order to establish a clear management plan.

An assessment of the maternal risk for major haemorrhage should be made as suitable blood for maternal transfusion may be difficult to source. If there is an increased likelihood maternal haemorrhage e.g. placenta praevia, previous postpartum haemorrhage or maternal anaemia, inform blood transfusion laboratory

2. Antenatal Screening

A sample for maternal blood group and red cell antibody screen should be routinely performed at the time of booking and at 28 weeks gestation. Please ensure that all samples are 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.

Subsequent antibody testing and fetal monitoring depends on the type and level of antibody (ies) present British Committee for Standards in Haematology (BCSH) guidelines suggest that. If anti-D, anti-c or anti-K antibodies are detected the frequency of testing should be increased to monthly until 28 weeks and then fortnightly until delivery

Red cell antibodies are found in around one percent of pregnancies. Up to 30% of clinically significant antibodies occur for the first time in the third trimester. Almost every clinically significant red cell antibody has been implicated in causing variable degrees of HDFN. However, the commonest cause of significant HDFN is anti-D, although the incidence of this is decreasing due to the routine use of anti-D immunoglobulin prophylaxis. 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 1).

3. Paternal Testing

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 (see below).

Paternal blood group and red cell phenotype should be determined where possible when antibodies that are associated with a risk of HDFN are present:

If the father's phenotype indicates that he is antigen negative: The fetus 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 another specificity develops further risk assessment and care should be initiated as per this guidance.

If the father's phenotype indicates that he is antigen positive: Paternal zygosity must be determined to estimate the risk of the fetus having the antigen(s) of interest.

If the paternal genotype suggests the father is homozygous for the antigen of interest: The fetus must carry the relevant antigen(s) and therefore can be affected by maternal antibody to that antigen. The fetus is considered 'at risk' and appropriate referral and management should be instituted. **Free fetal DNA testing is not required**.

If the paternal genotype suggests that the father is heterozygous for the antigen(s) of interest: The fetus may, or may not, carry the relevant antigen (s); free fetal DNA testing is required to establish the risk of the fetus having the antigen(s) of interest

If there is any uncertainty, or if the father of the baby is unwilling or unable to provide a blood sample, use free fetal DNA testing instead of paternal testing where available

The form accompanying such samples must clearly indicate the origin of the sample, the relationship to the woman with antibodies and the woman's name, date of birth and hospital &NHS number.

4. Free fetal DNA testing

Fetal red cell antigen status for D, C, c, E, e and K can be determined by analysing free fetal DNA from maternal plasma. Where these antibodies are implicated, a sample for free fetal DNA analysis is performed.

A maternal sample for free fetal DNA testing should be undertaken if the paternal genotype indicates that the father is heterozygous (or the genotype is unknown), and antibody to D, K, C, c, E or e is present.

If free fetal DNA testing suggests that the fetus is antigen negative: the fetus is 'not at risk' from this antibody and care should be as for a non-sensitised pregnancy, while continuing to monitor the antibody level and screen for **emergence of any new antibody.** It is important to remember that occasional false negative results have been reported using free fetal DNA testing. Therefore, if further routine antibody testing suggests a rising antibody level, consider the possibility that the fetus may in fact be antigen positive and seek fetal medicine advice.

If free fetal DNA testing suggests that the fetus is antigen positive: the fetus is 'at risk' of HDFN, and serial ultrasound scans and MCA –dopplers will be required. A referral should be made to WMFMC as per the guideline. Continue antibody testing monthly till 28 weeks and then fortnightly till delivery.

If paternal genotyping and/or free fetal DNA testing is not possible, provide care as if the fetus is antigen positive and therefore at risk from antibody to that antigen.

How to collect and send sample for free fetal DNA: 16mls EDTA Maternal blood to be sent (from 16 weeks for D,C,c,E & from 20 weeks for Kell/K) at room temperature within 48 hours of collection. Download request form from http://ibgrl.blood.co.uk

Where to send the sample: See appendix 3 for the address of the lab

anti-K antibody the anaemia may not be solely haemolytic in nature

Monitoring

Maternal Antibody Level:

Antibody levels are usually expressed as titres e.g. 1 in 4, 1 in 8, 1 in 64 etc. 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 therefore more clinical concern, for a titre of 1 in 64 than a titre of 1 in 4. Titres of >1 in 32 are usually taken as an indication for antenatal assessment

NB: In addition to causing haemolysis, anti-K antibody can also bind to red cell precursors in the bone marrow, suppressing fetal erythropoiesis, and contributing to fetal anaemia. Thus significant fetal anaemia may arise in the presence of lower levels of anti-K antibody. Therefore the presence of anti-K itself is interpreted as 'high risk'.

There is good correlation between low levels of antibody and a benign outcome; however, the outcome is more unpredictable at higher levels as the degree of haemolysis is also dependent on other aspects of the antibody. The level of antibody is therefore only an indication that more direct assessment of the fetus is required.

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

Where an antibody level, whether measured by titre or by quantification, indicates **moderate** risk of HDFN, and gestation has reached 16 weeks, an urgent referral should be made to WMFM centre to further investigation / assessment using Middle Cerebral Artery Peak Systolic Velocity (MCA PSV) Doppler scanning. If the antibody level suggests **'high risk'** MCA PSV Doppler scanning should be undertaken as soon as is practical in order to determine the presence and severity of fetal anaemia.

Table1 -Antibody levels and associated risk of HDFN:

Risk of fetal Aneamia	Antibody specificity & Level			
	Anti-D (iu/ml)	Anti-c (iu/ml)	Anti-K(titers)	Other Antibodies (Titre)
LOW	0-4	0-7.5	-	<1 in 32
MODERATE	4-15	7.5 -20	-	
HIGH	>15	>20	Positive	>1 in 32

*** Anti-K at low levels can lead to fetal anaemia and mother need to be urgently referred to WMFM.**

*** The presence of anti-E with anti-c increases the risk of fetal anaemia. Therefore, the patients with low levels of anti-c with anti-E need early referral.**

Feta Monitoring

Ultrasound scan (USS) & Middle Cerebral Artery (MCA) Doppler:

Serial USS may need to be performed to check for signs of fetal anaemia (e.g. ascites, pleural effusions, hydrops, placentomegaly) along with MCA PSV Doppler Study. MCA doppler should be performed by a suitably trained person and the result interpreted by a clinician with expertise in the management of HDFN. MCA PSV monitoring is predictive of moderate and severe anaemia 100% sensitivity and a false positive rate of 12%.

The fetus at moderate or high risk of HDFN

When antibody levels or obstetric history indicate moderate or high risk of HDFN prediction of fetal anaemia should be based on MCA Doppler assessment. MCA peak systolic velocities (PSV) of >1.5 Multiples of the Median (MoM) have good predictive value for moderate to severe anaemia As anaemia can develop rapidly, regular monitoring, at least fortnightly, is suggested.

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 present
- Any other antibody present at titre □ 1 in 32
- There is history of previously affected/treated pregnancy

Discussion with the WMFMC should take place in following situations and as per referral criteria –see below

- MCA PSV exceeds 1.5 MoM
- Antibody levels exceed the thresholds stated at less than 16 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
- MCA PSV Doppler Scanning is less sensitive for prediction of fetal anaemia beyond 36 weeks gestation. Decisions regarding timing of delivery should also take into account history, antibody level and MCA PSV trend.

The fetus at lower risk of HDFN

MCA Doppler is not indicated if maternal antibodies are present at levels below the thresholds outlined above (Table 1).

In all cases continue to monitor the antibody screen. The development of additional antibodies may alter the fetal monitoring regime and must be considered when providing appropriate (antigen negative) blood suitable for transfusion to mother or baby should the need arise.

Referral to WMFMC is indicated if there are ultrasonographic features suggestive of anaemia (e.g. ascites, pleural effusions, hydrops, placentomegaly)

Intra-Uterine Transfusion

Intervention using IUT is aimed at maintaining fetal haemoglobin at a level sufficient to prevent the adverse effects of anaemia and ultimately the development of hydrops. Development of hydrops can significantly worsen the prognosis. The Overall survival in affected babies has reported as 84% however non-hydrops babies have a survival of 94%. IUT is a highly specialised technique and is performed in Tertiary fetal medicine unit.

On referral to WMFMC women will be assessed and IUT offered if appropriate.

After 24 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.

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.

If IUT is required WMFMC will advise regarding timing of delivery based on estimated drop of haemoglobin at a unit with neonatal intensive care facilities.

Delivery

Delivery Plan

- The delivery plan should be documented as soon as is practical on the Clinical Care checklist Appendix 1.
- There is usually no additional need for elective caesarean section.
- 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.

- The delivery should take place in a unit with NICU facilities. The neonatal team should be involved in drawing up the delivery plan.

Women who have received IUT:

- Delivery is planned following discussion with WMFMC.

If no IUT has been necessary:

- Fetus at moderate or high risk, but MCA PSV less than 1.5MoM: Deliver between 37 and 38 weeks.
- Women with previous significant HDFN, but with MCA PSV less than 1.5 MoM: Discuss with WMFMC and deliver by 38 weeks in most cases.

  Women with high MCA PSV >1.5 MoM discuss with WMFMC then FBS assessment for IUT made
- Women with rapidly rising antibody levels at >36 weeks or high MCA PSV >1.5 MoM - all these cases should preferably be discussed with WMFMC as exchange transfusion may be considered. If it is felt that urgent review by tertiary centre fetal medicine consultant or local fetal medicine consultant is not be possible decision to deliver should be based on full clinical picture including steroid administration, fetal movements and CTG findings.
- Women with, anti-D <4 iu/ml or anti-c <7.5 iu/ml - Deliver between 37-38 weeks.
- Women with anti-K get advise from WMFMC.
- All other women: await spontaneous onset of labour

On 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 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.**

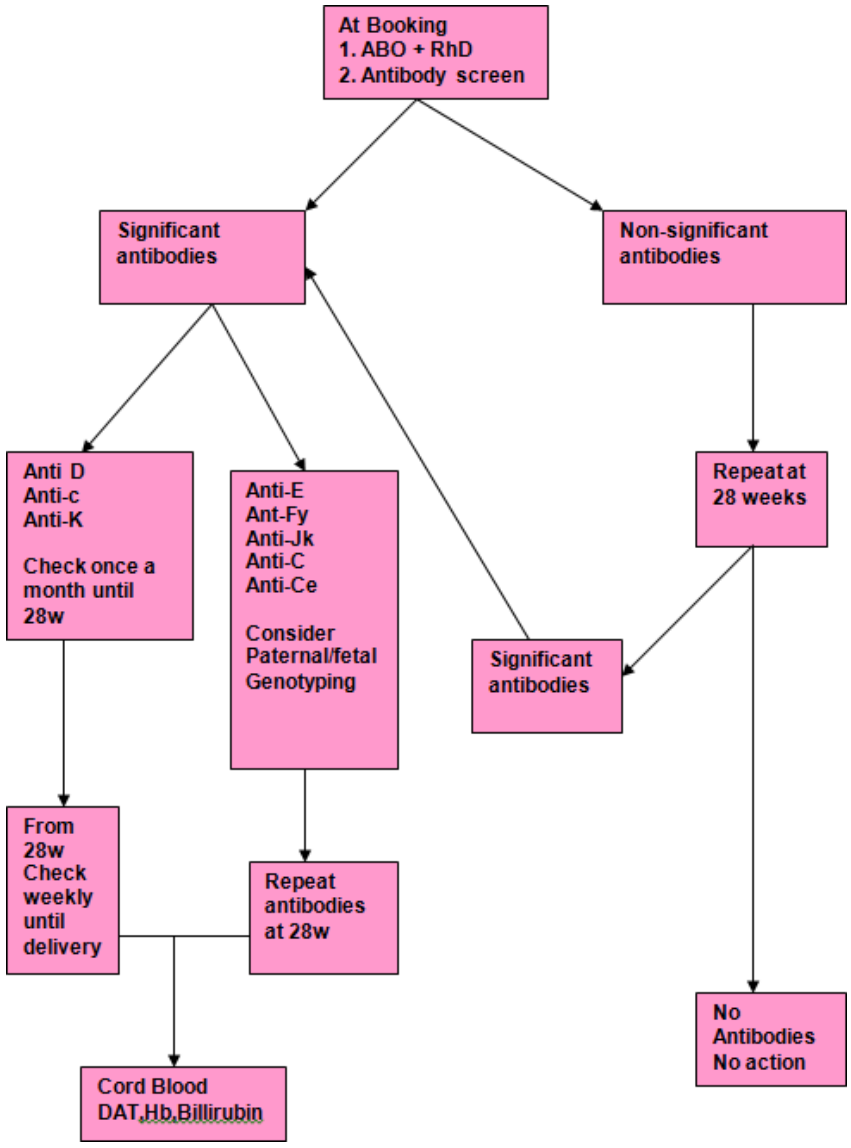
At Delivery

- 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 & RhD group, Direct Antiglobulin Test (DAT) and serum Bilirubin.
- Maternal blood should be taken for group and screen as soon as practical after delivery. Assessment of antibody level is not required at this stage.
- If a mother is RhD negative, and has not been sensitised to the D antigen, but is positive for other red cell antibodies, a maternal sample for Kleihauer test should also be taken. This sample should be taken at least 45 minutes after placental separation to allow distribution of fetal cells in maternal circulation. If the fetus is RhD positive anti-D immunoglobulin should be given in line with guideline
  WAHT-OBS-036

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

Timing and Frequency of Antibody Screening in Pregnancy

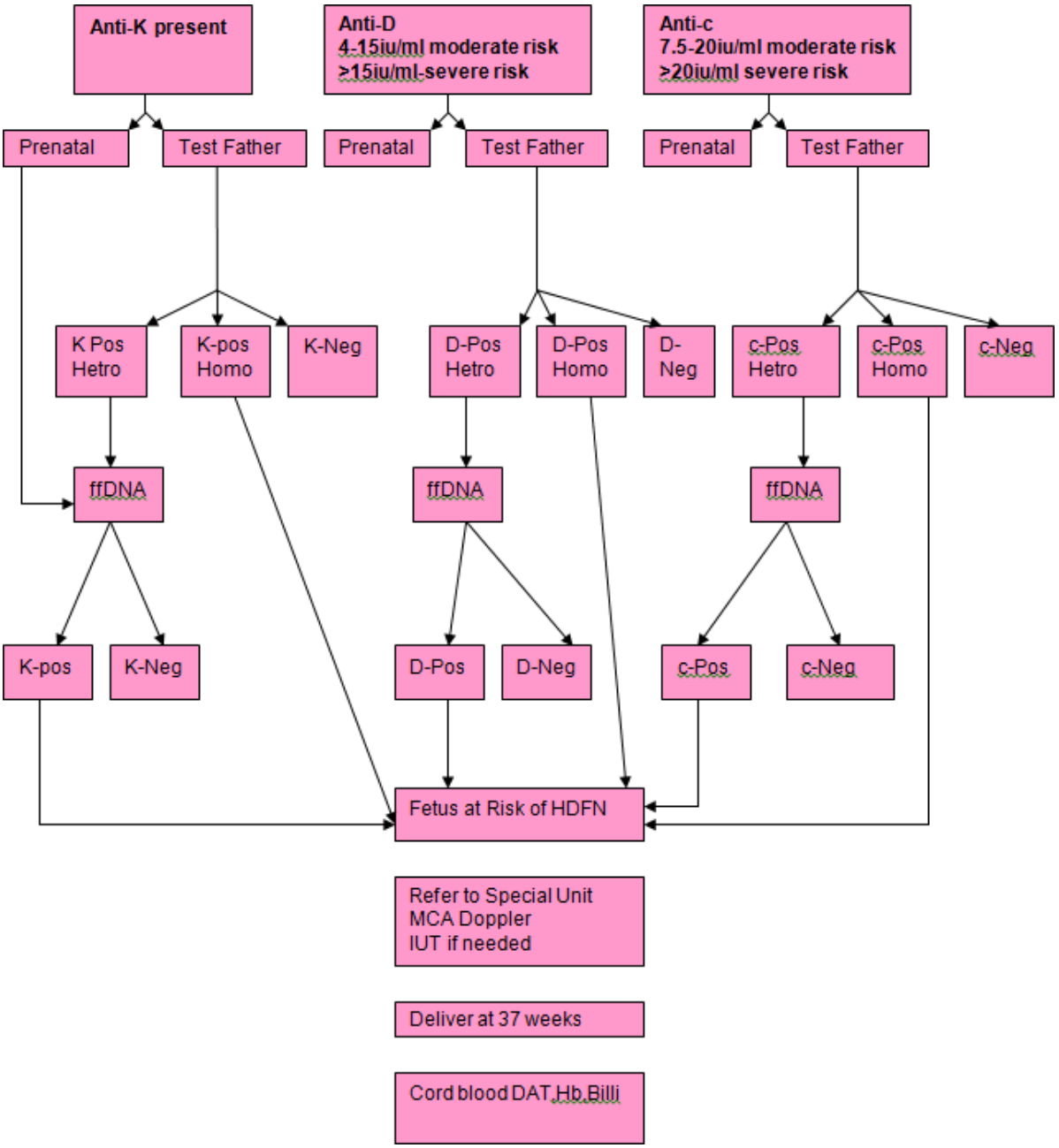


* Urgent referral to WMFMC If there is previous obstetric history or antibody levels indicate there is moderate risk for fetal anaemia.

*Presence of Anti-K needs urgent referral

Worcestershire Acute Hospitals NHS Trust

Management algorithm of pregnancies complicated with Anti-D, Anti-K or Anti-c alloimmunisation



Appendix 1 Useful Addresses

- **West Midlands Fetal Medicine Centre - Rhesus clinic**
  Fetal Medicine Team
  (Prof Kilby / Mr Martin)
  Birmingham Women's
  Hospital NHS Trust
  Metchley Park Road
  Edgbaston
  Birminghan
  B15 2TG
  Fax - 0121 627 2631 Phone – 0121 627 2683
  Referrals should contain a copy of all antibodies and scan results.

- **For enquiries regarding antibodies contact :**
  Dr Rekha Anand Consultant
  Heamatologist Birmingham
  01212784063
  01212534195

- **International Blood group reference lab (For free fetal DNA)**
  M Peter Martin
  NHS Blood Transplant, North Bristol Park
  Northway,
  Filton, Bristol.
  BS34 7QG Tel:
  01179217571
  pete.martin@nhsbt.nhs.uk