South Australian Perinatal Practice Guidelines

Red Cell allo-immuisation

Literature review

- Testing should be offered for blood group and Rh (D) status and screening should be offered for atypical red cell allo-antibodies (UK NSCPD 2006)
- Administration of anti-D at 28 and 34 weeks [as per NH&MRC Guidelines on the prophylactic use of Rh (D) immunoglobulin (anti-D) in obstetrics (2003)] may reduce sensitisation in a subsequent pregnancy of a Rh (D) negative women from 1 % to 0.2 %. Post delivery and other post sensitizing event assessment of fetal red cells by Kleihauer / flow cytometry with appropriate "top up" anti D administration may reduce sensitisation even further
- Rh iso-immunisation is becoming a comparatively rare cause of morbidity and mortality, having decreased to less than 6 per 1,000 live births, probably due to the routine use of Rh immunoglobulin (Crowther, Middleton 2009) and the reduction in family size over the past few decades
- Because of the relative rarity of Rh iso-immunisation, affected pregnancies should be managed by or in consultation with Maternal Fetal Medicine (MFM) subspecialists in a tertiary centre experienced in monitoring and managing iso-immunisation (ACOG 2006)
- In a centre with trained personnel and when the fetus is at an appropriate gestational age, Doppler measurement of peak systolic velocity in the fetal middle cerebral artery is a noninvasive and more appropriate method to monitor pregnancies complicated by red cell allo-immunisation than serial amniocentesis and spectrophotometric OD 450 measurement (Oepkes et al. 2006)

Clinical importance of red cell blood group antigens

Red cell groups causing iso-immunisation and severe haemolytic disease which may require antenatal fetal transfusion

- **D –** The Rh (D) antigen is the most common cause of severe red cell iso-immunisation. From 12 to 18 % of European, North American and Australian caucasians are Rh (D) negative. Between 2-5 % of Africans, and less than 3 per thousand Japanese and South East Asians are Rh (D) negative. Weak D expression, such as D^u, does not produce anti D iso-immunisation.
- **c - Anti** c antibodies against the Rh (c) antigen, are the next commonest cause. About 18 % of caucasians are c negative, about 50 % of Chinese, but it is rare in Africans. Perinatal mortality from anti c is about one 10^{th} of that from anti D
- **K –** Anti K (Kell) The most common immune red cell antibody outside the ABO and Rh systems. Anti K probably impairs haematopoiesis (Vaughan 1994) as well as causing haemolysis and peripheral sequestration. Hence, spectrophotometric analysis of amniotic fluid and antibody quantification as well as previous history are all unreliable in predicting how severely the fetus is affected. Consequently, neonatal hyperbilirubinaemia is less likely to be a severe feature of the disease. Fetal transfusion has also been reported as occasionally required because of iso-immunisation caused by Kell subgroups **k, -Kpa, -Kpb, -Jsa, Jsb, -Ula, - Ku and K22** (Daniels 1995)
- All other antibodies to the Rh systems (**C, E and e**) are capable of causing severe haemolytic disease, when present in high enough titre, but have less avidity and are less commonly implicated than **D and c**
- Other Rh- system antibodies that have been reported to cause severe haemolytic diseae include **anti ce (-f), -Ce, EW, -HrO, (-Rh17), -Hr, -Rh29, -Goa, -Rh32, - Bea, - Evans, Tar, and –Rh46** (Daniels 1995)
- **MNS system** – Most do not cause severe HDN, with the exception of **anti –S, anti –s, and anti – U**. Milder HDN from this group can occur from **Ena, Mia, Vw, Hut, Hil, Mta, Mv Far, and sD** (Daniels 1995)
- **Diego system** - Most do not cause severe HDN, with the exception of **anti -Dia .**

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Anti Dib may require neonatal exchange transfusion. **Anti Wra** and **anti – ELO** have both caused severe HDN (Better 1993)
- **Colton system – Anti -Coa** and **Anti -Co3** have both caused severe HDN (Savona 1989)
- **MAM** – the only high frequency antigen that can cause severe HDN (Montgomery1997)

Red cell groups causing milder haemolytic disease less likely (but still possible) to require transfusion

- Duffy (**Fya, -Fyb**). In a study of 68 pregnancies of **Fya** iso-immunised pregnancies, 10 were mildly and 3 severely affected, with 2 needing transfusion (Goodrick 1997). **Fyb** only very rarely results in haemolytic disease
- Kidd (**Jka, - Jkb**) – Rarely cause HDN. Occasionally result in neonatal jaundice sufficient to cause kernicterus
- Low frequency antigens – **Rd, -HJK, -Kg, -REIT, -JFV** and Jones have merited consideration of transfusion therapy. (Daniels 1995)
- **Vel, Lan, Ata** and **-Jra** have only caused mild haemolytic disease (Mollison 1997)

Red cell groups that do not cause haemolytic disease requiring fetal intervention

- **Lutheran (Lu)** – Rarely may cause mild HDN only (absorbed by the placenta, weakly expressed)
- **Lewis (Lea, Leb)** – Not expressed on fetal cells, not active at 37°C (Mollison 1997)
- **Anti Yt, Xg, Scianna, Dombrock, LW, Chido/Rogers, Gerbrich, Cromer, Knops, Indian, Kx, Ok, Raph, Cost, Er, Emm, AnWj, Sda, Duclos, PEL** and **ABTI** or any **HLA** antibodies have not been implicated in HDN (Daniels 1995)
- **ABO system** - although these antibodies can cause a severe haemolytic transfusion reaction, they are very rarely significant in regard to haemolytic disease of the newborn. This is probably because any antibody crossing the placenta is likely to become bound to placental tissue, and because the A and B antigens are poorly antigenic in the fetus even at the time of birth

Antenatal prediction of fetal blood group

Paternal blood group testing to predict the fetal blood group

- This is a sensitive topic, as it may be a mistake to assume that the partner is actually the father of the unborn baby. Subsequently, great care and tact are needed to handle this situation
- Identifying the paternal red cell blood groups can provide information regarding the likelihood of the fetus inheriting the antigen, and hence being at risk of haemolysis and anaemia
- In some blood groups, this is relatively reliable. For example, where there is a pair of antithetical (alternative) antigens such as in the Kell group, interpreting the phenotype is straightforward. A heterozygous phenotype (K+k+) would give a 50 % chance of inheriting the K+ gene, and a 50 % chance of being affected by the maternal anti-K

- Unfortunately in some blood groups and ethnic communities, it is less reliable. For example, paternal phenotyping for D is less useful, as there is no antigen antithetical to D. However, linkage disequilibrium between D and CE genes means that if anti D, - C, -c, -E and –e reagents are used, an estimate of likely homozygosity can be made. This approach is reasonably reliable in caucasians, but may be less so in non-caucasians because of differences in gene frequencies among different ethnic groups

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Maternal invasive testing to predict fetal blood group

- When the paternal phenotype is heterozygous for the blood group antigen, amniocentesis can be used to obtain a sample of amniocytes, which by polymerase chain reaction, can be analysed for fetal blood grouping for the Rh antigens and Kell groups (available at IMVS molecular pathology)

Maternal peripheral blood testing to predict fetal blood group

- Rh D testing of fetal DNA in maternal plasma has been used in the United Kingdom (International Blood Group of Reference Laboratory, National Blood Service, Bristol) and in the USA for both experimental management of rhesus iso-immunisation, and for more appropriately targeted anti D prophylaxis. This service is available on a trial basis in Australia from the Australian Red Cross DNA laboratory [NIPRA Rh Study]. Until it is fully validated, monitoring of maternal antibody titres and or anti-D quantitation with fetal surveillance should be continued in pregnancies with significantly high Anti D titres

Principles of surveillance in pregnancy

- Pregnant women with a history of iso-immunisation in a previous pregnancy from a clinically significant blood antigen (see above) should receive specialist care
- Detection of an antibody to a clinically significant red cell antigen (see above) should be followed by quantitation of the antibody (available at WCH) Generally, if the titre of a clinically significant antibody is less than 1:32, antibody titres (along with screening for additional antibodies) should be checked monthly up to 28 weeks and then fortnightly until birth (BCSH 1996). Provided the levels remain stable, delivery at term is recommended. The baby must still be monitored vigilantly for signs of postnatal jaundice, with early recourse to phototherapy and paediatric consultation
- If the antibody titre increases more than two-fold (e.g. from 1:2 to 1:8, or from 1:4 to 1:16), consultation with a maternal fetal medicine team is appropriate. A titre that reaches 1:32 or more, requires referral to a maternal fetal medicine team (a 1:32 titre approximates an anti D level of approximately 4 IU per mL, although this can vary among laboratories)
- It is important that the same pathology laboratory is used when monitoring antibody titrations, as inter laboratory differences can occur, limiting meaningful comparisons
- If the detected antibody is from the Kell group (see above), consultation with and / or referral to a maternal fetal medicine team should occur regardless of the antibody titre

Guidelines for fetal intervention

- Fetal death from iso-immunisation is exceptionally rare at less than 18 weeks. In the absence of hydrops, fetal blood sampling and intrauterine transfusion should not be undertaken at less than this gestation (Orlandi 1990)
- A guide to the timing of intensive monitoring and intervention is the so-named “rule of 10”. It implies that the need for intervention in the current pregnancy is likely to occur up to 10 weeks earlier than it was in the previous affected pregnancy (Whitfield 1970).
- Any indication of fetal hydrops observed during pregnancy in a woman with blood group antibodies is an emergency requiring immediate referral, assessment and intervention. Fetal blood sampling and, depending on gestational age, intrauterine transfusion or delivery of the baby should be undertaken as a matter of urgency.

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- As outcomes of treatment are significantly worse for hydropic than for non hydropic fetuses (Moise 2002), it is inappropriate to await signs of hydrops before considering fetal intervention
- Ultrasound Doppler velocimetry of the middle cerebral artery is currently the best method for the early detection of fetal anaemia and the need for and timing of fetal blood sampling. (Oepkes 2006)

Postnatal medical care

- After birth, suppression of the baby's erythropoiesis as a result of intra uterine transfusions may result in ongoing anaemia and the need for top up red cell transfusions for several weeks.
- Postnatal counseling of the parents should include accurate information on the likelihood of recurrence and future treatment outcomes, as well as a frank discussion of alternative options, including donor insemination from an antigen negative donor

Maternal Fetal Medicine referrals

- Consultations and appointments for clinical review of women with severe iso-immunisation are available via the switchboard of the Women's and Children's Hospital 08 8161 7000 (On call Maternal Fetal Medicine subspecialist, or the Maternal Fetal Medicine coordinator)

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Abbreviations

Rh	Rhesus factor
UK NSCPD	United Kingdom National Screening Committee Policy Database
NHMRC	National Health and Medical Research Council
MFM	Maternal Fetal Medicine
ACOG	American College of Obstetricians and Gynecologists
HDN	Haemolytic disease of the newborn
BCSH	British Committee for Standards in Haematology
IU	International units
mL	Millilitre(s)
IMVS	Institute of Medical and Veterinary Science
DNA	Deoxyribonucleic acid
USA	United States of America
FBS	Fetal blood sampling
IUT	Intra uterine transfusion
OD	Optical density

Version control and change history

PDS reference: OCE use only

Version	Date from	Date to	Amendment
1.0	21 Sept 10	current	Original version

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