Recommendation

Non-invasive foetal blood grouping using cell-free foetal DNA (cffDNA) from maternal plasma in alloimmunised pregnancies can be performed for *RHD* (D), *RHCE* (c and/or E) or *KEL*01* (K) with a false negative rate of <1%. These tests should be requested at the gestation advised by the reference laboratory used, by obstetricians or foetal medicine specialists who can explain the implications of the test findings having undertaken testing at the appropriate gestation (GRADE 1C).

4.6.2 | Fetal genotyping to guide anti-D Ig prophylaxis in non-immunised Rh D negative women

Before the availability of foetal genotyping, approximately 40% of Rh D negative women (40 000 in the UK per annum) would have been given anti-D Ig prophylaxis unnecessarily as they were carrying a D-negative foetus. Routine foetal *RHD* typing for all D-negative pregnant women has been introduced in Denmark, Finland and the Netherlands to allow selective use of anti-D Ig prophylaxis. This helps reduce unnecessary exposure of women and their foetuses to a blood product with reduction in costs related to the provision of anti-D Ig prophylaxis and tests related to fetomaternal haemorrhage.[15,19,20] This service is now provided by NHS Blood and Transplant (NHSBT) in England and the Welsh Blood Service (WBS) in Wales. The use of high- throughput, non-invasive prenatal diagnosis of foetal *RHD* status was recommended by the National Institute for Health and Care Excellence (NICE) in 2016 (http://www.nice.org.uk).

For mass throughput screening of all D-negative pregnant women, cffDNA testing for *RHD* is sufficiently accurate from 11 weeks' gestation with false negative rates of 0.1%–0.3%.[13–15,21] It is however advisable to test the foetal *RHD* status using a more sensitive and specific methodology at a later gestation for alloimmunised pregnant women as described above.

Recommendation

Fetal RHD typing using a high-throughput methodology in pregnant women who have not formed anti-D, as part of a screening program to target anti-D Ig prophylaxis, is sufficiently accurate for implementation from 11 weeks' gestation. The cost effectiveness of such testing is dependent on provision at a point in the antenatal care pathway that does not necessitate an additional visit (GRADE 1C).

5 | ANTENATAL TESTING PROTOCOLS

5.1 | Routine antenatal testing

All pregnant women should have blood samples taken early in pregnancy, at booking, typically by 10 + 0 weeks of pregnancy, for ABO and D group and for screening for the presence of red cell alloantibodies. When an antibody screen is positive, further tests should be carried out to determine the antibody specificity and significance (see Section 3).

All pregnant women, whether D positive or D negative, should have a further blood sample taken at the 28 week appointment for re-checking the ABO and D group and further screening for red cell alloantibodies.[1] D-positive women are just as likely as D-negative women to form antibodies (other than anti-D) late in pregnancy.[7,22]

Local policies must ensure that D-negative women who are eligible for routine antenatal anti-D Ig prophylaxis (RAADP) have the 28 week antibody screening sample taken before the first dose of RAADP is administered. Samples taken after the injection could result in passive anti-D being detected, which may be mistaken for immune anti-D, and conversely, potentially dangerous immune anti-D being mistaken for passive anti-D Ig[23] (see Section 5).

Late developing antibodies first detected after 28 weeks' gestation (i.e.: they were absent in a sample taken at 28 weeks), are less likely to cause clinically significant HDFN.[24,25] The introduction of RAADP has resulted in the detection of anti-D Ig in samples taken after 28 weeks' gestation from D-negative women.[26] Since it is not possible to differentiate between prophylactic anti-D Ig and immune anti-D until the latter has reached a high enough concentration in reference quantification to exclude the former, there is the potential for confusion between the two[23] (see Section 5.1).

Recommendation

All pregnant women should be ABO and D typed and screened for the presence of red cell antibodies early in pregnancy (at booking) and at 28 weeks' gestation.[1] In D negative women the 28-week sample should be taken before the administration of RAADP (GRADE 1B).

Recommendation

In pregnant women with no clinically significant red cell antibodies capable of causing HDFN present at 28 weeks' gestation, no further routine antenatal blood grouping or antibody screening is necessary (GRADE 1B) (Figures 1 and 2).

6 | RED CELL ANTIBODIES DETECTED IN PREGNANCY

Anti-D, anti-c and anti-K are the antibodies most often implicated in causing haemolytic disease severe enough to warrant antenatal intervention.[7] Pregnancies in women with a previous history of confirmed significant HDFN should however be considered at risk, and referral as early as possible to a foetal medicine specialist made regardless of the antibody specificity(ies) identified. In all other cases, follow-up testing protocols are dictated by the specificity and concentration of the antibodies identified. Regardless of antenatal follow-up regimens, antibody identification should always be performed to check for the

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