Distinguishing Passive from Immune anti-D in Pregnancy

Summary of Significant Changes
Change to Qpulse document reference numbers and NBS to NHSBT.

Purpose
To ensure that a uniform RCI Clinical Policy for distinguishing passive from immune anti-D in pregnancy is implemented throughout NHSBT.

Definitions
NICE - National Institute of Clinical Excellence
IAT – Indirect Antiglobulin Test
RCI – Red Cell Immunohaematology
BBTS/RCOG – British Blood Transfusion Society/Royal College of Obstetricians

Applicable Documents
See References at end of document
RCI Clinical Policy for distinguishing passive from immune anti-D in pregnancy

BACKGROUND

In pregnant women, anti-D detected in a blood sample may be either passively acquired, following anti-D immunoglobulin (anti-D Ig) given as prophylaxis, or immune anti-D endogenously produced following sensitisation with D positive red cells.

Distinguishing between passive and immune anti-D is clearly important for the clinical interpretation of serological results, so that appropriate advice can be given regarding anti-D prophylaxis for the mother and to avoid risk to the fetus from immune anti-D, ie everything should be done to protect the health of the pregnant woman as well as her fetus.

At present it is standard practice to administer anti-D prophylaxis to unimmunised D negative women following the known causes of sensitisation. Anti-D Ig may also be given as routine antenatal prophylaxis at 28 and 34 weeks in some Trusts. This is likely to become more widespread following the recent NICE recommendations.

Following an intramuscular injection of anti-D immunoglobulin, serologically detectable levels of anti-D are reached within minutes and peak within 72–84 hours. The half-life of passive anti-D immunoglobulin is approximately 3 weeks, but it may be detectable by serological tests for up to 8 weeks by IAT and up to 12 weeks (and in exceptional cases up to several months) by the use of continuous flow analysers used for anti-D quantitation.

Immune anti-D is produced following sensitisation. Immune anti-D may become detectable 4 weeks after exposure to D-positive red cells, and generally reaches a peak after 6–8 weeks.

Both passive and immune anti-D may be detected either by enzyme techniques only, or by enzyme techniques as well as IAT, and cannot be distinguished. While passive anti-D levels will fall with time, immune anti-D levels will usually remain stable or rise if there is re-stimulation of the antibody. Where the level of anti-D is >1.0 IU/mL, a rise of >50% over the previous quantitated level, is a significant increase and suggests sustained immune anti-D production.

The risk of misinterpreting passive and immune anti-D is clear; if passive anti-D is misinterpreted as immune, anti-D prophylaxis may be omitted leading to sensitisation. If immune anti-D is misinterpreted as passive, appropriate follow-up of the antibody level may be curtailed putting the fetus at risk.
1. **Administration of Anti-D**

1.1 Advise administration of anti-D Ig according to BBTS/RCOG Guidelines. In particular, obstetric units, GPs, midwives and Early Pregnancy Units (EPUs) should be reminded that anti-D Ig is NOT required following first trimester bleeding in a viable pregnancy. In these cases prophylaxis is indicated only if there is doubt about the period of gestation or there is another clinical indication.

1.2 Trusts should be advised to record the administration of anti-D Ig in the patient’s notes.

1.3 Where supplies of anti-D Ig are provided to EPU, labour ward etc, Trusts should have a procedure in place to ensure that the transfusion laboratory/pharmacy receives feedback regarding the ultimate fate of this blood product.

2. **Information provided to RCI laboratories.** All requesters should be advised to complete the NHSBT request forms fully and to provide full details regarding anti-D Ig administration i.e date/s of administration and dose.

3. **Clinical Advice when <1.0 IU/mL anti-D is detected**

3.1 When information is provided that prophylaxis has been given in the 8 weeks prior to sampling, this is likely to be passive anti-D. In these cases, advice regarding follow-up testing and Rh prophylaxis should be as for unimmunised pregnant women.

3.2 Where information is not provided that prophylaxis has been given in the eight weeks before the blood sample was taken: anti-D levels up to 1.0 IU/mL may be due to immune or passive anti-D. The requester should be advised to check if prophylaxis has been given and advised that: if anti-D immunoglobulin has been given, the anti-D detected is most likely to be passive. In these cases follow-up tests and Rh prophylaxis should be advised as for unimmunised pregnant women.

3.3 Where the requester confirms that prophylaxis has not been given in the preceding 8 weeks or the information is unreliable, tests should be undertaken 4 weekly to 28 weeks and 2 weekly after 28 weeks. If the anti-D becomes undetectable by IAT, it is safe to assume that the anti-D previously detected was passive; advice regarding follow up (or not) and Rh prophylaxis should be as for unimmunised women. If anti-D remains detectable by IAT longer than 8 weeks after the last anti-D Ig injection, the antibody is likely to be immune and follow-up testing should be advised as for immunised women.

3.4 NB. The above guidance applies when only one standard dose of anti-D Ig (500IU or 1250IU) has been given. Following a >1250IU dose, passive anti-D may persist for longer. Following larger doses passive anti-D may be detectable by IAT for longer periods.

4. **Clinical advice where >1.0 IU/mL is detected**

4.1 If the anti-D level is **1.0 IU/mL or greater**, it is likely (but not certain) that it is immune. Check if the woman has been given a recent high dose of prophylactic anti-D. Recommend repeat serological testing by IAT and quantitation 4-weekly to 28 weeks and 2-weekly after
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28 weeks gestation (by IAT and quantitation) to identify fetuses and infants at risk of haemolytic disease.

Caution!

It should be noted that rarely, it has been known for the anti-D quantitation to be as high as 6.0 IU/mL following a standard dose of anti-D Ig. Passive anti-D may be detected for up to 12 weeks following a standard dose of anti-D Ig.

IAT results, rather than anti-D quantitation, provide the most reliable information to distinguish passive from immune anti-D.

5. If routine antenatal Rh prophylaxis is known to have been given at 28 weeks further follow-up tests are generally required only if the woman has anti-Kell. BCSH Guidelines do not mandate testing unimmunised woman after 28 weeks. Many hospitals test all unimmunised pregnant women including those who are D negative only once in the third trimester. There is no evidence that this policy is unsafe.

6. Passive and immune anti-D are indistinguishable by serological tests and notwithstanding these clinical Guidelines, critical clinical judgement must be exercised in all cases and at all times before advice is provided.

7. While there is doubt about the origin of the anti-D, anti-D prophylaxis should be advised.

8. Antibody cards. Antibody cards should be issued only once it is certain beyond doubt that this anti-D is immune.

References


Abstract: Eklund J, et al. Anti-D IgG was injected into 15 Rh-negative women in the 28th week of gestation and into three non-pregnant women. The recovery in vivo of anti-D was an average 24% in the non-pregnant women and 21% in the pregnant women. The half life of anti-D was 24 and 21 days, respectively. With a dose of 125 micrograms the plasma anti-D concentration was less than 1 ng/ml at about 10 weeks after the injection. With double the dose the concentration at delivery was at least 1 ng/ml. Although 250 micrograms of anti-D IgG seems to be effective when given in the 28th weeks of gestation, the great individual variations in uptake and recovery rates will lead to occasional cases of Rh-immunisation during pregnancy despite all routine regimens.

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