Immune or prophylactic anti-D – what do the new BCSH antenatal guidelines say?

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UK NEQAS (BTLP)
RAADP at 28 (+/- 34 weeks)

- Sensitisations and neonatal deaths due to anti-D
- Testing dilemmas!
Effect of anti-D Ig on transfusion testing in pregnancy

• Antibody screening
  – Panel of D negative cells covering clin. sig. antigens
  – Not suitable for EI if blood required
    • Positive antibody screen

• Where anti-D identified - ?immune or passive
Anti-D kinetics

- Immune anti-D detectable approx. 4 weeks after exposure to D+ cells, and reaches a peak concentration at 6-8 weeks

- Anti-D Ig peak concentration post i.m. at 3-7 days
- Pharmacokinetic study in pregnant women 1500IU anti-D Ig
  - iv was equivalent to 0.4IU/mL
  - im equivalent to 0.2 IU/mL
- Half-life of anti-D Ig is approx. 3 weeks
- Anti-D Ig rarely > 0.4 IU/mL unless >1500 IU given
- Detectable for 12 weeks & in exceptional cases several months
## Anti-D Ig product and dose

### What product is used for anti-D Ig prophylaxis?

<table>
<thead>
<tr>
<th>Anti-D Ig products</th>
<th>BPL D-Gam</th>
<th>CSL Rhophylac</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAADP</td>
<td>41%</td>
<td>56%</td>
</tr>
<tr>
<td>Post delivery</td>
<td>68%</td>
<td>31%</td>
</tr>
<tr>
<td>PSE &lt;20 weeks</td>
<td>86%</td>
<td>14%</td>
</tr>
<tr>
<td>PSE &gt;20 weeks</td>
<td>69%</td>
<td>31%</td>
</tr>
</tbody>
</table>

### What dose is used for anti-D Ig prophylaxis?

<table>
<thead>
<tr>
<th>Dose anti-D Ig</th>
<th>250 IU</th>
<th>500 IU</th>
<th>1500 IU</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAADP</td>
<td>-</td>
<td>3%</td>
<td>95%</td>
<td>2%</td>
</tr>
<tr>
<td>Post delivery</td>
<td>-</td>
<td>66%</td>
<td>33%</td>
<td>1%</td>
</tr>
<tr>
<td>PSE &lt;20 weeks</td>
<td>71%</td>
<td>14%</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>PSE &gt;20 weeks</td>
<td>(1%)</td>
<td>66%</td>
<td>32%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Organisational questionnaire, 147 sites

Slide from Megan Rowley
Bottom line...

- Potential for >1500IU anti-D
  - 2010 NCA 14% RAADP given i.v.

- Cannot differentiate immune and prophylactic anti-D serologically
Risks

• Immune anti-D, assumed to be passive
  – Pregnancy not monitored appropriately, and chance of early intervention to prevent or reduce HDFN missed

• Passive anti-D Ig, assumed to be immune
  – Anti-D prophylaxis may be withheld, risking sensitisation to the D antigen, and HDFN
SHOT data 2011

• 8 misinterpretations of immune anti-D as anti-D Ig
  – 1 weak antibody screen not followed up ? anti-D Ig
  – 7 cases no record of anti-D Ig having been administered
    • 1 a reference laboratory had already reported an immune anti-D

• Appropriate monitoring did not take place
  – 1 required an emergency intrauterine transfusion (IUT)
  – 2 neonates required top up post-delivery
  – 3 born with symptoms of HDFN but no Tx required
  – 2 unaffected
• If record of anti-D Ig in past 8 weeks and the antibody reaction is weak, test as for non-sensitised women i.e. no antibody testing after 28 weeks and Rh prophylaxis should continue.

• If no record of anti-D Ig or information re prophylaxis, the antibody should be monitored by both IAT and anti-D quantification as for immunised women.
  – If the anti-D becomes undetectable by IAT and the quantified level is falling it is probably passive. A rising or steady level indicates immune anti-D.

• If there is significant doubt re immune or passive refer for quantification.

• Anti-D prophylaxis should continue unless it is established beyond doubt that the anti-D is immune.
13E10 UK NEQAS ‘standard’ anti-D

- Includes labs testing by a single technology (once or more than once) where the group includes at least 12 laboratories.
12E6 UK NEQAS screening reactions recorded (UK and ROI)

- P2 and P4 same pool of anti-c
- 20/390 (5%) variable reaction strengths
- 18 x 1 strong and 1 weak
- 2 x 1 weak and 1 negative
BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn (Quereshi et al)

Transfusion Medicine, 2014, 24, 8–20

• Regardless of any prior administration of anti-D Ig, any anti-D detected at 28 weeks should be quantified and the results made available in the maternity notes
• Further history should be obtained and investigations undertaken to establish whether this is immune or passive
• If no clear conclusion can be reached as to the origin of anti-D, then prophylaxis should continue to be administered in accordance with guidelines for D negative women who have not formed immune anti-D
# Anti-D Ig for PSEs

<table>
<thead>
<tr>
<th>Potentially sensitising event</th>
<th>Cases</th>
<th>Correct dose</th>
<th>Correct time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum haemorrhage</td>
<td>438</td>
<td>92%</td>
<td>79%</td>
</tr>
<tr>
<td>Miscarriage &amp; Stillbirth</td>
<td>278</td>
<td>92%</td>
<td>77%</td>
</tr>
<tr>
<td>Fall/trauma</td>
<td>198</td>
<td>91%</td>
<td>83%</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>49</td>
<td>88%</td>
<td>65%</td>
</tr>
<tr>
<td>External cephalic version</td>
<td>47</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>49</td>
<td>88%</td>
<td>65%</td>
</tr>
<tr>
<td>In-utero procedure</td>
<td>11</td>
<td>82%</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1052</strong></td>
<td><strong>92%</strong></td>
<td><strong>79%</strong></td>
</tr>
</tbody>
</table>
BCSH antenatal guidelines
(2014 *in draft*) History

- All efforts should be made to determine whether anti-D Ig has been given and why, i.e. as RAADP or following a PSE, by asking the woman & seeking written confirmation in the notes.
BCSH antenatal guidelines (2014 *in draft*) Testing

- Prediction re immune / passive anti-D should not be made on reaction strength as this can be unreliable.

- All anti-D detected in pregnancy should be quantified, or tested by a method that has been extensively validated against quantification, e.g. using a titration score [Bruce *et al* 2013]).

- *(one exception - where detected for the first time immediately prior to delivery)*
BCSH antenatal guidelines (2014 *in draft*) **Exception**

- Anti-D detected (1\textsuperscript{st} time) immediately pre-delivery
  - No quantification required as results unlikely to influence clinical decisions at this stage
  - Baby monitored for signs of HDFN. Maternal anti-D quantification may be performed at a later stage if deemed necessary.
If *all* of the following apply, then testing should be as for non-sensitised women:

- There is a written record of administration of anti-D Ig in the preceding 8 weeks.
- The antibody screen was negative prior to the administration of anti-D Ig.
- The concentration of anti-D is <0.2 IU/mL.
If *any* of the following apply, then monitor as for immunised women

- there is no written record of anti-D Ig administration
- anti-D was present before the administration of anti-D Ig
- the concentration of anti-D is .....  
  - ? Dependent on dose of anti-D Ig, ?timing, ?route of admin
  - ? Set value
If in doubt – continue anti-D prophylaxis! *(common to all guidance)*

- Whilst the concentration of passive anti-D will fall with time, the concentration of immune anti-D will remain stable or rise if there is re-stimulation.

- Anti-D prophylaxis should continue to be offered as required for RAADP or PSEs, unless it is *conclusively established* that the anti-D is immune, in which case anti-D prophylaxis may be discontinued.
BCSH antenatal guidelines
(2014 *in draft*) Clinical context

- The quantification results should be viewed in the context of the timing and dose of any anti-D Ig given previously, the reason for its administration, and the antibody status at the time of administration.
- The clinical history and knowledge of the results of previous laboratory testing are paramount in clinical decision making where anti-D is detected in pregnancy, and every effort should therefore be made to obtain this information.
Impact of future initiatives on immune or passive anti-D dilemma

cfDNA testing - targeting anti-D Ig to women carrying a D pos fetus

? RAADP in second trimester

Monoclonal anti-D Ig
? method developed to discriminate between this and immune anti-D
BCSH Antenatal guidelines

• To sounding board by end of Nov
• ? Published early 2015
• Writing group:
  – White J, Qureshi H, Massey E, Needs M, Byrne G, Daniels G, Allard S.