Haemolytic Disease of the Fetus and Newborn

Janet Birchall
Case history

- 30 yr old in 2\textsuperscript{nd} pregnancy, EDD 14/1/16
- Booking – no \( \alpha D \)
- 27+4 antibody screen + prophylactic 1,500iu \( \alpha D \)
  Antibody +ve \( \alpha D \) \( \rightarrow \) flow cytometry. 0.4iu/ml
  Report “may be passive or immune. Continue prophylaxis & monitor as immune”
- Pregnancy remained under midwife care
- 33+4 \( \alpha D \) 0.3iu/ml. Report 4/12/15 “suggestive of immune origin, continue monitoring”
- 37+3 labour, sample \( \alpha D \)
- Following day discharged
- Day 3 post delivery, \( \alpha D \) 87iu/ml
  Baby re-admitted – bilirubin 600
Case history, continued

- Treatment x2 ex tx units
- Now abnormal posture and EEG. MRI shows ↑ signal basal ganglia.
- Likely long term neurological damage
Figure 6.2 Mechanism of RhD Sensitisation during the 1st Pregnancy

ABC of Transfusion, 3rd Edition. Edited by Marcela Contreras
Haemolytic disease of fetus & newborn

- Range in severity - detectable only in laboratory → infant with anaemia/jaundice → stillborn
- Risk of significant fetal anaemia low in 1st affected fetus
- Severity ↑ with each subsequent pregnancy
ABC of Transfusion, 3rd Edition.
Hydrops Fetalis, Medulla, Infant with Kernicterus
Mothers, babies and blood. 25th January 2017

The impact of Anti-D Ig

- Introduction of Anti-D prophylaxis
- Improved obstetric care
- Currently 15-25 deaths per year
Significant RBC antibodies

• What is the antibody
  • many antibodies capable of causing HDFN
  • anti-D,-c,-K cause the most serious disease

• How active is the antibody
  • antibody level/titre
  • past history of HDFN
Determination of antibody titre or level

**Titration:**
- Serial dilution compared in parallel with previous sample
- Titre = reciprocal of the highest dilution → agglutination
- Inherently imprecise, reliant on experienced personnel

**Quantitation:** anti-D and anti-c
- Autoanalyser - more automated, greater reproducibility
1. Reagent cells (D or c +)
2. Bromelin + Methyl cellulose
3. Patient plasma (anti-D /c)
4. Flow through circuit of autoanalyser
5. Agglutinated cells precipitate
6. Unagglutinated red cells flow through
7. Lysis of unagglutinated cells
8. Absorption measured in photometer
Guideline for blood grouping and red cell antibody testing in pregnancy

At booking
- All pregnant women
- ABO + D* typing
- Antibody screen

Clinically significant** antibody screen positive
- Anti-D, -c or -K***
  - Consider paternal/fetal genotyping for corresponding antigen(s)
  - Test monthly until 28 weeks gestation
  - See figure 2

From 28 weeks gestation:
- Test 2 weekly until delivery
- See figure 2

Cord blood for:
- DAT, Hb, bilirubin

No clinically significant** antibodies
- Repeat testing at 28 weeks gestation

No antibodies
- No further action

Clinically significant antibodies
- Consider paternal/fetal genotyping for corresponding antigen(s)
Antibody level and risk of HDFN

anti-D iu/ml
- <4 - low
- ≥ 4 - mod
- >15 - high

anti-c iu/ml
- <7.5 - low
- ≥7.5 - mod
- >20 - high

other abs - HDN unlikely when titre <32
Haemolytic disease due anti-K

Anti-K

- ↓ fetal erythropoiesis → ↑ anaemia ↓ haemolysis
- often transfusion induced
- check husband’s K type
  - if Kk or unknown monitor monthly/2 weekly
  - If “confirmed father” K-ve (91% K –ve) ↓ monitoring
ABO HDFN

- ABO incompatible infants have ↓Hb, ↑bilirubin
- more common in Asia, ME, S. America
- maternal anti-ABO titre not predictive
- neonatal jaundice is first sign and prompts investigation
- usual O mother and A or B baby
- first incompatible infant is affected in 50% of families

If prev h/o ABO HDN
- consider fetal monitoring in subsequent pregnancy
- hospital delivery
- cord ABO gp, DAT, bilirubin, Hb (baseline)
- do not discharge early
- community midwife to monitor baby
Fetal Medicine Unit

• Refer FMU
  – Level/titre anti-D ≥ 4 or c ≥ 7.5, other antibody titre ≥ 32
  – rising level
  – previous history of HDFN

• Investigation
  – partner homozygous/heterozygous? If heterozygous consider fetal genotyping of maternal blood for D (c,K)
    Caution father or partner?
  – ? evidence of fetal anaemia
Tests used by obstetricians to predict fetal anaemia

**Ultrasound**
- placental thickness
- umbilical vein diameter
- liver length
- spleen perimeter

**Doppler**
- measure fetal blood flow - middle cerebral artery

- useful to assess fetal maturity
- does not identify early fetal disease - changes visible only once hydrops has occurred
- weak correlation with fetal Hct/Hb

- detects early fetal anaemia
At birth if DAT +ve monitor bilirubin & Hb

Consensus-based bilirubin thresholds for the management of babies of 38 weeks or more gestational age with hyperbilirubinaemia

<table>
<thead>
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<th>Age (hours)</th>
<th>Bilirubin measurement (micromol/litre)</th>
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<tbody>
<tr>
<td>0</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>6</td>
<td>&gt; 100, &gt; 112</td>
</tr>
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<td>12</td>
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<td>&gt; 237, &gt; 287</td>
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<tr>
<td>96+</td>
<td>&gt; 250, &gt; 300</td>
</tr>
</tbody>
</table>

Action

- Repeat bilirubin measurement in 6–12 hours
- Consider phototherapy and repeat bilirubin measurement in 6 hours
- Start phototherapy
- Perform an exchange transfusion unless the bilirubin level falls below threshold while the treatment is being prepared.
Exchange transfusion pathway

Offer information to parents and carers about exchange transfusions and intravenous immunoglobulin (IVIG) including:
- why the treatment is being considered
- anticipated duration of treatment
- possible adverse effects
- when it will be possible for parents or carers to see and hold the baby
- the need to admit the baby to intensive care for an exchange transfusion (if needed)

During exchange transfusion do not:
- stop continuous multiple phototherapy
- perform a single-volume exchange
- use albumin priming
- routinely administer intravenous calcium

Prepare for exchange transfusion
- Initiate/maintain continuous multiple phototherapy
- Use IVIG (500 mg/kg over 4 hours) for babies with Rhesus or ABO haemolytic disease if serum bilirubin level rises by more than 8.5 micromol/litre/hour

Serum bilirubin level falls to below threshold for exchange transfusion

Baby has:
- bilirubin level that remains above threshold for exchange transfusion and/or
- clinical signs of acute bilirubin encephalopathy

Continue multiple phototherapy and perform exchange transfusion

Continue multiple phototherapy and measure bilirubin level within 2 hours of exchange transfusion and manage according to threshold table and treatment threshold graphs

Go to ‘Manage hyperbilirubinaemia’ box in ‘Investigation pathway’ (see pages 10–11)
Summary

• RBC survival ↓ by placental transfer of maternal antibody
• Clinical severity ranges from unaffected to stillborn
• Mortality ↓ since 1950’s from detection, prevention, monitoring and antenatal & neonatal intervention
• HDFN from Anti-D, anti-c, anti-K > other antibodies
• Low risk1st affected pregnancy. Risk ↑ future pregnancies
• Serology – detect at risk pregnancy & monitor mild HDFN
• FMU if > mild HDFN or previous history
• AN intervention – IUT or delivery
• PN intervention - phototherapy, IVIG, Ex. transfusion