Obstetric Management of Sensitised Pregnancies

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Advances in obstetric management of RhD allo-immunisation

- Spectacular 30 fold drop in deaths from Haemolytic disease of the newborn since routine administration of Anti-D to RhD negative mothers after delivery in 1970
- Non-invasive assessment of anaemia of the fetus by Ultrasound -2000
- Free fetal DNA from maternal plasma can be used to ascertain fetal RhD genotype 2002
RhD allo-immunisation

- IgG antibodies to RhD Antigen will persist in the circulation and the numbers of antibodies can be multiplied hugely if there is repeated contact with these foreign RhD red cells (amnestic response).
- IgG Antibodies are small molecules and cross freely into the placenta.
- If the fetal cells are RhD positive they are targeted by the IgG molecules and are destroyed by the fetal Reticulo-endothelial system (HAEMOLYSIS) which may lead to ANAEMIA.

Red Cell Allo-immunisation

- Consequence is haemolytic disease of the fetus and newborn (HDFN).
- Features are anaemia, jaundice, hepatosplenomegaly.
- If severe then fetal HYDROPS can develop in utero.
- Fetal Demise may follow.

How have deaths decreased?

Prevention is better than cure………..

- Anti-D administered after all deliveries
- Anti-D administration for sensitising events
- Routine Ante-natal Anti-D Prophylaxis

NB Anti-D for sensitisation events accounts for 99% of prevention of sensitised pregnancies.
How are sensitised pregnancies caused?

- 99% of sensitisations occur after a sensitisation event which was not prevented (or given inadequate prevention)
- Routine Antenatal Anti-D Prophylaxis will prevent only 1% of cases
- It is far more effective to treat sensitisation events properly than to use RAADP

Deaths have decreased from HDN

Cure..................
- Less frequent amniocentesis now
- Less frequent in-utero transfusions
- Increasing sub-specialisation

Because
- More effective and less invasive means of detecting fetal anaemia than amniocentesis

Fetal Hydrops

- Fluid in peritoneal cavity
- Skin oedema
- Usually associated with deficit of 7g/dL for gestational age
- Often levels of about 4g/dL
Fetal Hydrops
- Fluid in pleural cavity
- Fluid in peritoneal cavity
- Mechanism not clear
- ? Decreased osmotic pressure of blood
- ? Heart failure

Red Cell Allo-immunisation
- Commonest is the rhesus (D) antigen
- Cc Ee (from Rhesus classification)
- Kell
- Duffy (Fy)
- Kidd (Jk)
Population data for the Rh D factor and RhD allele

<table>
<thead>
<tr>
<th>Population</th>
<th>Rh D Neg</th>
<th>Rh +ve</th>
<th>Rh –ve Alleles</th>
</tr>
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<tbody>
<tr>
<td>European Basques</td>
<td>35%</td>
<td>65%</td>
<td>60%</td>
</tr>
<tr>
<td>Other Europeans</td>
<td>16%</td>
<td>84%</td>
<td>40%</td>
</tr>
<tr>
<td>African descent</td>
<td>&lt;1%</td>
<td>&gt;99%</td>
<td>3%</td>
</tr>
<tr>
<td>Asian</td>
<td>&lt;1%</td>
<td>99%</td>
<td>1%</td>
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16% Women in UK are RhD Neg
- About 65,000 RhD +ve babies born to RhD –ve women per year (10% of all births)
- Chances of her partner being homozygous for Rhesus D antigen are 39%.
- Chances of her partner being Rh Neg are 16%
- Chances of her partner being a heterozygote is 46% so chances of Rh pos baby or Rh neg in these situations is 50% each
- Therefore there is a 61% chance of an Rhesus +ve fetus
Sensitised Pregnancies

- 90% will not require intra-uterine transfusions….but we have to monitor them all
- Total number of fetuses in England and Wales with HDFN is only 500/year
- Of this number 25-30 will die
- 5% mortality
- 2% loss from intra-uterine transfusions

History of RhD in Obstetrics

- 1940 – Landsteiner and Weiner demonstrate the Rhesus antigen
- 1941 – Liley charts invented (to help to monitor Haemolytic disease of the fetus)
- 1968 – Anti-D given to Rh neg women routinely after delivery
- 1978 – Routine Antenatal Anti-D Prophylaxis developed
- 1990 – Deaths due to Haemolytic disease of newborn have decreased from 46/100,000 pre-1969 to 1.8 per 100,000

National Guidance on Anti-D Administration

- RCOG Green-Top Guidelines 2002
- NICE Guidance –Technology Appraisal of Routine Antenatal Anti-D Prophylaxis August 2008
Sensitisation Events

- Miscarriage after 12 weeks
- Termination of pregnancy (medical or surgical) at any gestation
- Amniocentesis or CVS or fetal blood sampling
- Evacuation of the products of conception

Sensitising Events

- Birth
- Ante-partum haemorrhage
- External Cephalic Version
- Abdominal Trauma
- Ectopic Pregnancy

Events leading to an increased chance of significant FMH (>4mls)

- Traumatic deliveries including caesarean section
- Manual removal of the placenta
- Stillbirths and intrauterine deaths
- Abdominal trauma during the third trimester
- Twin pregnancies (at delivery)
- Unexplained hydrops fetalis
**Dose and Timing of Anti-D Immunoglobulin**

- Before 20 weeks – 250 iU of Anti-D asap
- After 20 weeks – 500 iU of Anti-D asap

A KLEIHUER test will quantify the bleed and should be performed after delivery.

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**Situations where Anti-D is NOT needed - RCOG 2002**

- Complete miscarriages or threatened miscarriages under 12 weeks
- Any sensitised woman at any time
- 10 days or more AFTER the sensitising event
- Possibly useful – recurrent threatened miscarriages < 12 weeks; heavy/repeated; abdo pain

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**Situations where it IS needed**

- A potential sensitisation event will need (more) Anti-D immunoglobulin even if a routine Antenatal Anti-D dose has been given recently
- Ref. RCOG Green-Top Guideline 2002
Have we got our policy right?

- In other countries, a routine single dose of 1,500 IU im Anti-D is given after delivery. This will cover a FMH of up to 12mls.
- UK policy is to give 500IU and to check the Kleihauer test for the level of fetomaternal haemorrhage.
- More Anti-D IgG is given if needed.
- The current regime will cover a FMH of 4mls ie 99.2 – 99.3% of women.

Quantification of size of FMH

- Kleihauer – should be taken within 2 hours of delivery or sensitising incident.
- Rosetting Technique.
- Flow Cytometry.

NICE Guidelines – August 2008
RAADP – Technology Appraisal

- Routine Antenatal Anti-D Prophylaxis
- Anti-D should be administered at 28 and 34 weeks of pregnancy (500IU im)
- OR
- Single dose regime
- 1500 IU im at 28-30 weeks
- Dose regime should be purely on basis of COST because no significant difference in prevention of Allo-immunisation.
**Effect of Routine Antenatal Anti-D Prophylaxis**

- Without RAADP, about 1% of women would be sensitised.
- 650 per year.
- About 550 of these would go on to have another baby.
- These would need close monitoring.
- 10-12% would need intra-uterine transfusion.
- £42k to £120k cost per baby saved.
- £3k to £8K per sensitisation avoided.

**Costs of different regimes**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Single dose</th>
<th>2 dose</th>
<th>2 dose course</th>
</tr>
</thead>
<tbody>
<tr>
<td>500iU D-Gam</td>
<td>£35 per 1250 prefilled syringe</td>
<td>£27 per vial</td>
<td>£54 per 2 dose course</td>
</tr>
<tr>
<td>Rhophylac</td>
<td>£46.50 per 1500IU</td>
<td>£46.50 per 1 dose regime</td>
<td></td>
</tr>
<tr>
<td>Partobulin</td>
<td>£70 per 2 dose course</td>
<td></td>
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**Routine Antenatal Anti-D Prophylaxis - 2005 Survey**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Single dose</th>
<th>2 dose</th>
<th>2 dose course</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>25%</td>
<td>60%</td>
<td>15%</td>
</tr>
<tr>
<td>500iU at 28 and 34 weeks</td>
<td>500iU at 28 weeks</td>
<td>1500 iU at 28 weeks</td>
<td></td>
</tr>
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</table>
Safety and Acceptability of Anti-D

- Anti – D IS a blood product
- Implications for Jehovah’s Witnesses
- US donors since 1998 (no risk of nvCJD)
- Donors are screened by history (lifestyle)
- Donors plasma is tested
- Virus inactivation and removal
- No viral transmissions since 1970s

How are sensitised pregnancies managed?

- Women who are Rh neg and sensitised are defined at booking with antibody level
- Refer to obstetrician for Risk Assessment
- History of previous IUD/ hydropic pregnancies or need for intra-uterine transfusions or exchange transfusions are highly significant
- Group partner. If Rh +ve – zygosity testing
- If Heterozygote – can test for free fetal DNA in the maternal plasma

First Scientific and Clinical Breakthrough – Free fetal DNA

- The MATERNAL blood can now be tested to determine the FETAL Rh status
- Free fetal DNA is present in the maternal plasma
- DNA amplification will allow testing of the fetal Rh group
- Cost - £212 per test
Free Fetal DNA
Pre-natal determination of fetal rhesus D status by DNA amplification of peripheral blood of Rh Neg mothers – Ann N Y Acad Sci 1994 Lo et al

Management of sensitised pregnancies
- If low, the Antibody Titre will be repeated every 4 weeks until 28 weeks
- Fortnightly measurements thereafter
- Urgent notification of obstetrician if rapidly rising titre
- Critical Level – 15 IU/ml
- This must prompt referral to a fetal medicine unit to monitor for fetal anaemia

What is the evidence for a critical level of 15mU/mL?
- Maternal Antibody level and Assessment of Rh Isoimmunisation -Nicolaides and Rodeck –BMJ 1992
- N=237. Blood taken by cordocentesis (N=144) or by fetoscopy (N=93)
- In ALL 42 pregnancies with Ab level of <15 IU/ml the fetuses were mildly anaemia at most
- In the hydropic fetuses the Ab level was always >15IU/mL
Second breakthrough – Dopplers of fetal brain vessels to detect anaemia

- Moderate or severe anaemia in fetuses can now be reliably diagnosed NON-INVASIVELY
- Saves unnecessary procedures
- Saves fetal lives

Invasive and Non-invasive Methods of assessing for fetal anaemia

- Middle Cerebral Artery Doppler
- Amniocentesis for bilirubin level (indirect measurement of fetal haemolysis) – now out-dated
- Cordocentesis (direct Hb measurement and transfusion if needed)

How does blood flow in the Middle Cerebral Artery alter in an anaemic fetus?

- Fetuses suffering from hypoxia will preferentially divert blood to the brain
- Anaemia will result in a low blood viscosity and a higher cardiac output
- ALL blood vessels in the fetus will show high blood velocities but the Middle Cerebral Artery shows this to exaggerated effect
- It is also easy to measure
Middle cerebral artery – Peak Systolic Velocity

- Middle cerebral artery
- Easy to access
- Easy to get 0° angle
- Consistency easily maintained
- 1.5 Multiples of Median is positive
- Sensitivity – 95 - 100%
- Specificity – 85%

Middle Cerebral Artery Dopplers – Compare and Contrast

- Left picture MCA Doppler from a severely anaemic fetus
- Right picture shows a normal MCA Doppler waveform

Original Research on MCA Dopplers in 1990s

- Diagnosis of fetal anaemia with Doppler ultrasound complicated by maternal blood group immunisation
  Mari et al Ultrasound Obstet Gynaecol 1995

- Delta OD450 and Doppler velocimetry of the middle cerebral artery peak velocity in the evaluation for fetal alloimmune disease: Which is best?
Landmark RCT - 2000
- Mari et al – Randomised Controlled Trial
- 111 Women enrolled who were to have a fetal blood sample because of high titres of red cell antibodies
- They looked at Peak Systolic velocities of the MCA
- Found that using an MCA cut-off of 1.5 MoMs would accurately predict ALL cases of significant fetal anaemia
- More accurate and safer than amniocentesis

Research Evidence for Accuracy of Doppler of MCA
- Ultrasound in Obs and Gynae 2004 23(5)432
- Sheirer et al – MCA Dopplers in 83 women with high titres of antibodies (15IU/mL)
- Compared with 813 normal controls
- A cut off of 1.5 Multiples of Median for Peak Systolic Velocity accurately predicted ALL fetuses with significant anaemia

Further Confirmation
- Bullock et al US O&G 2005
  Prediction of fetal anaemia in pregnancies with red-cell alloimmunisation: comparison of MCA PSV and amniotic fluid OD450
- Oepkes et al Am J O&G 2004
  Minimally invasive management of Rh alloimmunisation: Can Amniotic Fluid delta OD450 be replaced by Doppler studies? A prospective randomised trial.
Historical Methodology - Amniocentesis and Liley Charts

- Amniocentesis in sensitised at risk pregnancies
- Amniotic fluid analysed with photospectrometry
- Change in optical density indicated bilirubin level and (indirectly) level of anaemia

Have Liley Charts outlived their usefulness? Nicolaides, Rodeck et al, 1986

Queenan Charts
Advantages of more direct measurement of fetal anaemia

- More useful for KELL alloimmunised pregnancies
- Kell antibodies compromise erythroid precursors as well as causing haemolytic anaemia
- Also can use MCA Dopplers for detection of anaemia due to parvovirus (B19)
- More accurate and SAFER

Management of delivery of Sensitised pregnancies (continued)

- MCA Dopplers are less reliable after 36 weeks
- Plan to induce at 38 weeks generally
- Allo-immunisation is NO INDICATION FOR CS per se
- Fetal outcome is expected to be good even after several intra-uterine transfusions

Case History – Queens Hospital 2008

- Ms W, EDD 3/12/08
- 18 year old P1G2. Rh Negative
- Previous pregnancy – TOP for fetal abnormality at about 36 weeks – Ventriculomegaly and agenesis of the corpus callosum
- Given Anti-D Kleihauer test done after Delivery - No fetal cells and no need to give further Anti-D
Current Pregnancy

- Booked in first trimester
- Booking Bloods showed several red cell allo-immune antibodies: Anti-D, Anti-Kell, Anti-C, Anti-e, Anti-Jkb – all low levels
- Anti-D titre rose to >300 iU/mL at 27 weeks
- Other antibodies’ titres did not rise
- Referred to tertiary referral centre for transfusion
- Planned for close monitoring of MCA Dopplers

Graphic Representation of Ab levels in Ms W

<table>
<thead>
<tr>
<th>Gest Age</th>
<th>7w4d</th>
<th>11w+3</th>
<th>16w+1</th>
<th>20w-0</th>
<th>24w-0</th>
<th>28w-0</th>
<th>31w+2</th>
<th>36w-5</th>
<th>33w-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>24/4</td>
<td>25/6</td>
<td>19/6</td>
<td>16/8</td>
<td>15/8</td>
<td>15/8</td>
<td>31/10</td>
<td>6/10</td>
<td>28/10</td>
</tr>
<tr>
<td>Anti-D Level (iu/mL)</td>
<td>3.5</td>
<td>5.2</td>
<td>5.9</td>
<td>5.9</td>
<td>5.5</td>
<td>&lt;300</td>
<td>1.13</td>
<td>1.05</td>
<td>1.05</td>
</tr>
<tr>
<td>Fetal Transfusion 28.30.33</td>
<td>16/9</td>
<td>60 mins</td>
<td>Tightly</td>
<td>23/9</td>
<td>70 mins</td>
<td>11/16</td>
<td>11/16</td>
<td>0/11/16</td>
<td></td>
</tr>
</tbody>
</table>

Cordocentesis and blood transfusion

- Aim for cord insertion through the placenta
- Take initial Hb
- Give Rh Neg blood
- Irradiated and CMV negative XMatched with Maternal blood
- Tightly packed cells (75-90%)
- 2% fetal loss rate
- 20% loss if hydrops already
Ms W……continued
- Referred to Kings College Hospital at 29/40
- High MCA Dopplers (x2 MoMs)
- Given intra-uterine infusion at 29 weeks then subsequently at 30, then at 33 weeks (final)
- Technically difficult in this patient
- Pregnancy continued to be monitored by measurement of the MCA at Queens Hospital
- Delivery at 36 weeks by Caesarean Section
- Baby 3 kg, fared well , Hb 12g/dL

Burden of Monitoring and anxiety
- Blood assays every month then fortnightly
- Twice weekly DAU monitoring when sensitised
- MCA Dopplers every week
- MCA Dopplers become less reliable after 36 weeks
- Delivery early in this patient because technically difficult procedures
- Intra-uterine transfusions X3
- Mother extremely anxious

The future
- Free Fetal DNA used to determine fetal genotype – available at Southmead Hospital currently – cost £212 for test
- Improvements in COMPLIANCE with current guidelines of NICE and RCOG
- Improvements specifically with taking Kleihauer to quantify FMH at delivery
- Increasing sub-specialisation to improve fetal loss rates with intra-uterine transfusions