Fetal anaemia: Why is it still a headache?

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Introduction:

- 50 Different antibodies
- 3 associated with severe fetal disease
  - Anti-Rhesus (Rh) D 85%
  - Anti-Kell (K1) 10
  - Anti-Rhc 3.5%
- Rarely a cause of a problem:
  - Anti-E
  - Anti-Fa (Duffy)
Prevalence of Rh(D)

- Caucasians 15%
- Africans 5%
- Japanese and Asians < 1%
- Basques 30 to 35%
Pathogenesis:

- Rh(D) antigen expressed on fetal RBC membrane by 30 days gestation
- 0.1ml of fetal blood enters the maternal circulation in nearly all pregnancies
- The immune response varies considerably among individuals
- 1% women will develop anti-D antibodies
- 7-9% antibodies within 6 months
Pathogenesis:

- The percentage of patients who will develop antibodies depends on:
  - The volume
  - Immunogenicity of the fetal RBC
  - Immunogenic response of the mother

- Antibodies are detected 5 to 15 weeks after immunization.
Pathogenesis:

- Severity of fetal anaemia depends on:
  - Anti body titre
Pathogenesis:

Other factors:

- Subclass and glycosylation of maternal antibodies
- Structure, site density, maturational development and tissue distribution of blood group antigens
- Efficiency of transplacental IgG transport
- Functional maturity of fetal spleen
- Polymorphisms affecting Fc receptor
- Presence of HLA-related inhibitory antibodies
Pathogenesis: Rh(D)

- ABO –incompatibility protects
- RhD immunoglobulin reduces Rh allo-immunization from 16.5 to 2.7 per 1000 cases
- 50% of neonates slightly affected
- 25-30% moderate anemia
- 20-25% severely affected
Anti-Rhc

- Member of the Rh family
- Hackney et al:
  - 25% of antigen-positive neonate had severe haemolytic disease of the fetus/neonate (HDFN)
  - 7% hydropic
  - 17% required intra uterine transfusions
Rhc, RhE, Rhe

- Rhesus family
- Low titre in combination with anti-RhD
- Contributory effect
- As only finding Joy and co-workers found:
  - Total of 32 pregnancies
  - 1 fetus hydropic
  - 15% evidence of mild fetal or neonatal anemia.
RhG

- When the Anti-RhC titres equals or higher than Anti-RhD
- Usually associated with mild to moderate HDFN
- NB: Give RhD immunoglobulin if an invasive procedure is done.
24 members but only 8 associated with HDFN

- Kell (K, K1)
- Penny (Kpa, K3)
- Rautenberg (Kpb, K4)
- Peltz (Ku, K5)
- Sutter (Jsa, K6)
- Matthews (Jsb, K7)
- Karhula (Ula, K10)
Anti-K

- Kell protein similar to protein family of zinc neutral endopeptidases
- Plays important role in red-cell growth and differentiation.
- Fetal anaemia the result of:
  - Sensitization of antigen positive cells with subsequent sequestration in the fetal reticuloendothelial system
  - Erythropoietic suppression
Anti-K

- 9% of Caucasians
- 2% people from African descent
- 5% risk of a severely affected fetus
- 8% risk of mild HDFN
Duffy

- Two antigens
  - Fya
    - 66% Ag + Caucasians; 26% HZ
    - 10% Ag + Africans; 90% HZ
  - Fyb not associated with HDFN
  - Low titre 1:8 associated with HDFN requiring transfusion
Causes of trans placental bleeding

- Miscarriage
- Ectopic
- CVS
- Amniocentesis
- Multiple pregnancy
- Abdominal trauma
- APH
- ECV
- Caesarean section
- Manual removal of the placenta
- Normal vaginal delivery
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First pregnancy:

- Difference in 1 dilution is still accepted
- Repeat every 4 weeks
- Anti-D 100µg at 27-28 weeks and 32-33 weeks
- Anti-D 100µg when increased risk of transplacental bleeding
First affected pregnancy

- Maternal titre < 1:8 repeat monthly until 24 weeks and the every two weeks until delivery
- Once critical titre of 1:16 is reached refer for evaluation to determine if fetal anaemia.
Determine fetal Rh

- Cell free fetal DNA
  - PCR
  - Accuracy between 94.8 and 98.7%
  - Presence of fetal DNA confirmed by
    - SRY gene
    - Single nucleotide polymorphisms
  - False positive the result of a pseudogene or another Rh(D) gene variation
Determine fetal Rh

- More than one Rh(D) region is tested for

- False negative results can be due to:
  - Lack of fetal DNA
Determine fetal Rh status

- Amniocentesis
  - PCR on uncultured amniocytes
  - Rare discrepancies between fetal genotype on amniocytes and phenotype of erythrocytes.
Assessment for fetal anemia

- Middle cerebral artery-peak systolic velocity:
  - Sensitivity 86-100%
  - False Positive Rate 10 to 18%
  - After 35 weeks the false positive rates increases
  - It should be measured in the resting stage
Assessment of fetal anaemia

- Spectral analysis of amniotic fluid
  - Only if expert sonography not available
  - Once critical titre is reached
  - Bilirubin present in the amniotic fluid gives indication of anemia.
  - Queenan curve sensitivity 81% specificity 81%
  - Every 10 to 14 days
Management of Rh-D alloimmunized pregnancy

Homozygous phenotype

- Do serial fetal MCA Dopplers Q 1 - 2 weeks
  - MCA < 1.5 MoM’s
    - Continue weekly MCA Dopplers
    - Induce delivery in 2 weeks (37 - 38 wks EGA)
  - MCA > 1.5 MoM’s
    - Intrauterine transfusion if fetal Hct < 30%

Heterozygous phenotype

- Amnio for AOD₄₅₀ and fetal lung maturity
  - Mature; AOD₄₅₀ below upper Rh+, affected OR intrauterine transfusion zone
    - Induce delivery in 2 weeks (37 - 38 wks EGA)
  - Immature; AOD₄₅₀ IN upper Rh+, affected OR intrauterine transfusion zone
    - Administer maternal Phenobarbital (30 mg po TID); induce in 7 days
  - Immature; below upper Rh+, affected OR intrauterine transfusion zone
    - Repeat amnio in 14 days
    - Induce delivery in 2 weeks (37 - 38 wks EGA)

RhD negative, paternity assured

- Amnio at 15 weeks to
- Repeat amnio in 7 weeks
- Induce delivery in 2 weeks (37 - 38 wks EGA)
Management of non-Rh-D alloimmunized pregnancy
Intra uterine transfusion

- Sir William Liley first introduced the concept
- Based on African children with sickle cell disease who got intra peritoneal infusions.
- Sonography not available
- Fetal position determined by techniques like:
  - Radiopaque dye to delineate fetal bowel
  - Placing metal markers on maternal abdomen
  - Inserting needles to immobilize the fetus
Intra uterine infusion:

- 1975: Static gray scale ultrasonography and IUT
- 1977: Real time
- 1981: Intravascular
Intra uterine transfusion

- For patients at risk of severe anaemia:
  - MCA Vmax > 1.5MoM

- Before 18 weeks a technical challenge

- After 35 weeks procedure greater risk than delivery
Indications

- Red cell alloimmunization
- Parvovirus infection
- Chronic fetomaternal hemorrhage
- Inherited RBC disorders
- Complications after treatment of twin-twin transfusion syndrome.
Blood for transfusion

- Preparation:
  - Type O Rh negative
  - CMV antibody negative
  - Fresh blood
  - Irradiation 25 Gy of gamma radiation
  - Leukodepletion
  - Units are washed and tightly packed
Choice of access site

- Peritoneal cavity
  - Good absorption prevented in the hydropic fetus
  - Option in early pregnancy or when access is difficult
Choice of access site

- Umbilical cord
  - Optimal site in umbilical vein near cord insertion
  - Increased risk of bradycardia if:
    - Free loop
    - Uterine artery
    - Cord insertion close to fetal insertion
Choice of access site

- Intrahepatic umbilical vein
  - Advantages
    - Less Bradicardia
    - Blood loss can be reabsorbed
  - Disadvantages
    - More fetal pain
    - Fetal movement may cause organ damage
  - Fetal anaesthesia
Special circumstances

- Early gestation or poor visualisation:
  - Intra peritoneal transfusion
- Fetal ascites:
  - Intrahepatic vein
  - In the cord
  - Intra cardiac
- Multiple gestations:
  - Intrahepatic vein - Choice of access site
Volume of transfusion:

- Volume transfused (mL) = Volume of fetoplacental unit (mL) \times (final - initial hematocrit) divided by the hematocrit of the transfused blood.

- Fetoplacental volume (mL) = 1.046 + fetal weight in grams \times 0.14.
Volume for intra peritoneal transfusion

- Volume (mL) = (gestational age – 20) X 10.
blood transfusion through the umbilical vein in the placenta

ultrasound transducer

placenta

umbilical cord

fetus

pubic bone

uterus

vagina
cervix

spine

http://www.sogi.net.au/mintdigital.net/SOGI.aspx?XmlNode=/Services/Fetal+Treatment/Intrauterine+transfusion
Timing the transfusion

- Decline in fetal hematocrit after first transfusion 1% per day
- Follow up transfusion in 10 to 14 days
- After 3 or more transfusions the interval can be stretched to 3 to 4 weeks
- Threshold for further transfusion decreases to 1.3 MoM.
Medical management

- Phenobarbital 30mg tds po for 10 days after the last transfusion
- Trevett et al:
  - Significantly fewer neonatal exchange transfusions
  - Adjusted relative risk 0.23, 95% CI 0.06-0.76
Risk of IVT

- Perinatal death 1.6% per procedure (%pp)
- Emergency caesarean section 2.0%pp
- Infection 0.3 %pp
- Premature rupture of membranes 0.1%pp
- Inadvertent arterial puncture 3%
- Bradycardia or tachycardia 5%pp
- Total procedure related risk: 3.15
- Infection
- Cord or visceral trauma
Risk of IVT

- There is a risk of the mother developing new antibodies as a result of the transfusion

- Maternal autologous transfusion is possible

Benefits
- Decrease in the total number of transfusions
- Fewer transfusion to the neonate
Prevention of sensitization

- First and second trimester
  - 50-100µg
- Third trimester
  - 100µg at 27 – 28 weeks and 32-33 weeks
- Post delivery
  - Massive bleeding
  - Kleihauer-Betkhe test
  - 25ml fetal blood needs 300µg anti D
# Management post delivery

<table>
<thead>
<tr>
<th>Neonate</th>
<th>Mother</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh(D) negative</td>
<td></td>
<td>No action</td>
</tr>
<tr>
<td>Rh(D) positive</td>
<td>Coombs positive with titre ≥1:8</td>
<td>Sensitization already occurred</td>
</tr>
<tr>
<td>Rh(D) positive</td>
<td>Coombs positive with titre &lt; 1:8</td>
<td>Anti-D globulin 300µg within 72 hours</td>
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Parvo B19

- Small non-enveloped DNA virus
- Single-stranded DNA genome with 5000 nucleotides
- 35-55% of pregnant women has IgG antibodies.
- 50% risk for household contacts and 20-30% for classroom contacts
- 3.3-3.8% of infection during pregnancy
Parvo B19

- Slapped cheeks appearance not as common in adults
- Systemic symptoms 1-4 days prior to rash
- Arthropathy last 1 to 2 weeks
- In patients with sickle cell or thalassemias there is a risk of an aplastic crisis.
Fetal risk with Parvo B19

- Risk of fetal loss before 20 weeks is 11%
- Risk of fetal loss after 20 weeks is 1%
- Transient risk of effusions
- Risk of fetal hydrops 3.9%
- Severe thrombocytopenia 37%
PARVO B19

- Severe Parvo B19 associated anemia:
  - Reduced survival of the red cells
  - Need to meet red cell demands of expanding intravascular volume
  - Inability of immune system

- Miocardial infection
PARVO B19

- History of suspected infection or exposure
- Maternal IgM and IgG
- Do PCR on amniotic fluids
- Follow up MCA Vmax
- Have platelets ready for transfusion
Conclusion

- Why is it still a headache?
  - Women are at risk of developing iso-immunisation despite anti-D immunoglobulin administration
  - Some women do not receive anti-D after miscarriage or ectopic pregnancies.
Conclusion

- Women should have regular titres done throughout pregnancy
- With intensive fetal surveillance a good outcome can be achieved.