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 considerable among individuals
- 1% women will develop anti-D antibodies
- 7-9% antibodies within 6 months

Pathogenesis:

- The perentage of patient 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 aneamia
- 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.

Kell

- 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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WHY STILL A HEADACHE?

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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 trans placental 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 psuedogene 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

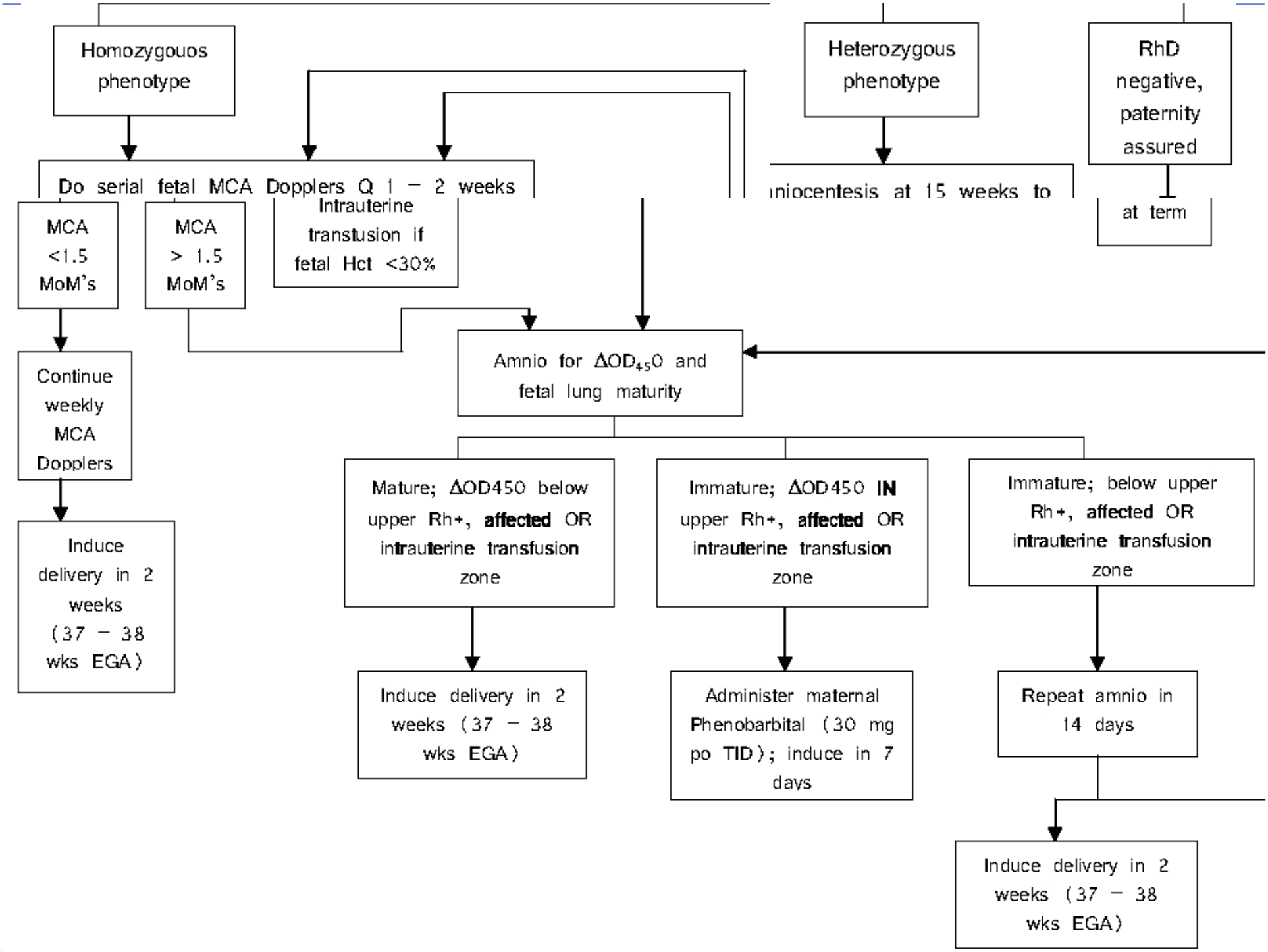
- Amniocentesis
  - PCR on uncultured amniocytes
  - Rare discrepancies between fetal genotype on amniocytes and phenotype of erythrocytes.

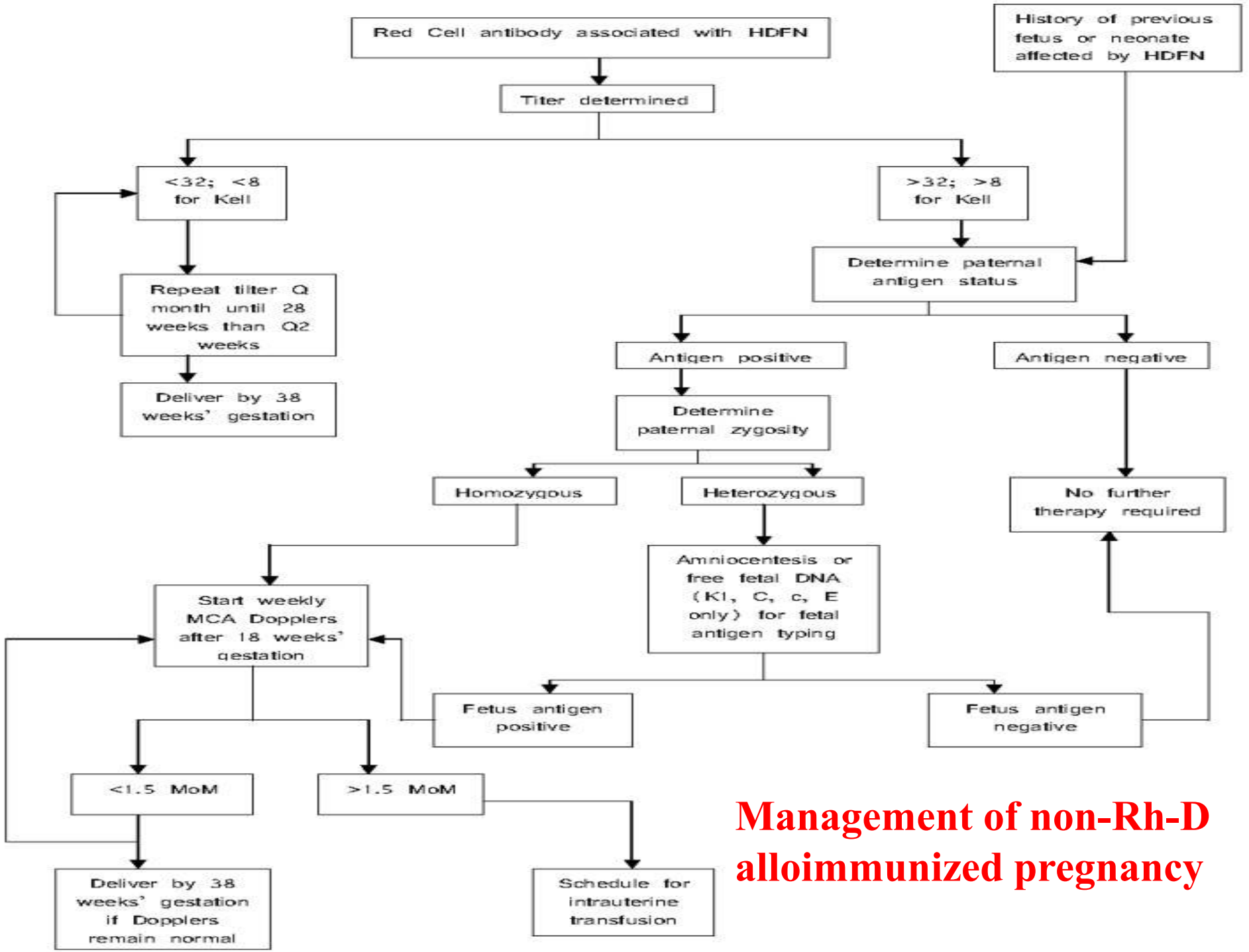
Assessment for fetal aneamia

- 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


Homozygouos phenotype
Heterozygous phenotype
RhD negative, paternity assured
Do serial fetal MCA Dopplers Q 1 – 2 weeks
niocentesis at 15 weeks to
at term
MCA <1.5 MoM's
MCA > 1.5 MoM's
Intrauterine transtusion if fetal Hct <30%
Continue weekly MCA Dopplers
Induce delivery in 2 weeks (37 – 38 wks EGA)
Amnio for ΔOD450 and fetal lung maturity
Mature; ΔOD450 below upper Rh+, affected OR intrauterine transfusion zone
Immature; ΔOD450 IN upper Rh+, affected OR intrauterine transfusion zone
Immature; below upper Rh+, affected OR intrauterine transfusion zone
Induce delivery in 2 weeks (37 – 38 wks EGA)
Administer maternal Phenobarbital (30 mg po TID); induce in 7 days
Repeat amnio in 14 days
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 wit 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 $\geq$ 1.5MoM
- Before 18 weeks a technical challenge
- After 35 weeks procedure greater risk than delivery

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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

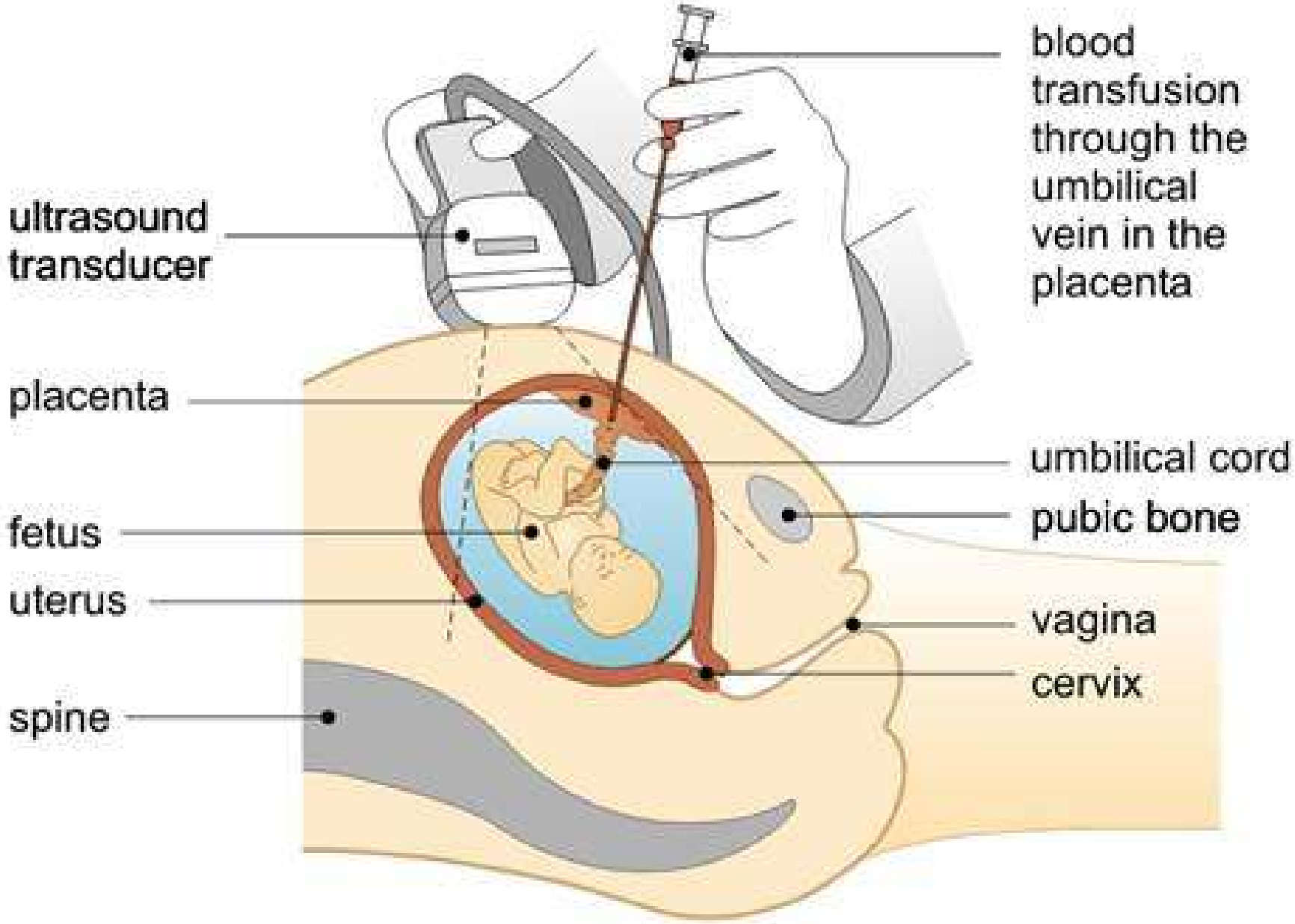
Volume of transfusion:

- Volume transfused (mL) = Volume of fetoplacental unit (mL) x (final – initial hematocrit) devided by the hematocrit of the transfused blood.

- Fetoplacental volume (mL) = 1.046 + fetal weight in grams x 0.14.

Volume for intra peritoneal transfusion

- Volume (mL) = (gestational age – 20) X 10.



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

Neonate	Mother	Action
Rh(D) negative		No action
Rh(D) positive	Coombs positive with titre $\geq$1:8	Sensitization already occurred
Rh(D) positive	Coombs positive with titre < 1:8	Anti-D globulin 300µg within 72 hours
Rh(D) positive	Coombs negative	Anti-D globulin 300µg within 72 hours

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

Conlcusion

- 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 through out pregnancy
- With intensive fetal surveillance a good outcome can be achieved.