

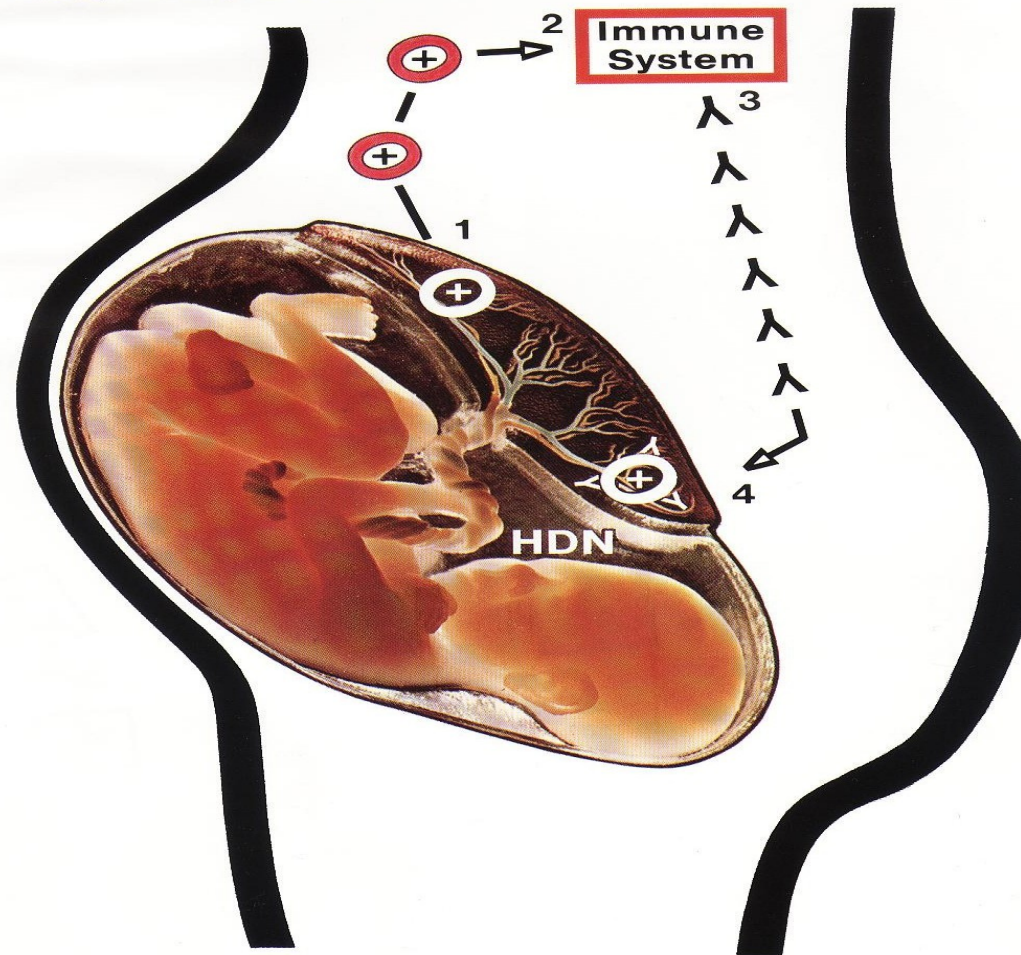
Haemolytic Disease of the Foetus and New Born

Dr R Anand

HDF & N

(HDF&N) destruction of the (RBCs) of the fetus/neonate by antibodies produced by the mother (maternal alloantibodies formed against red cell antigens acquired from the father)

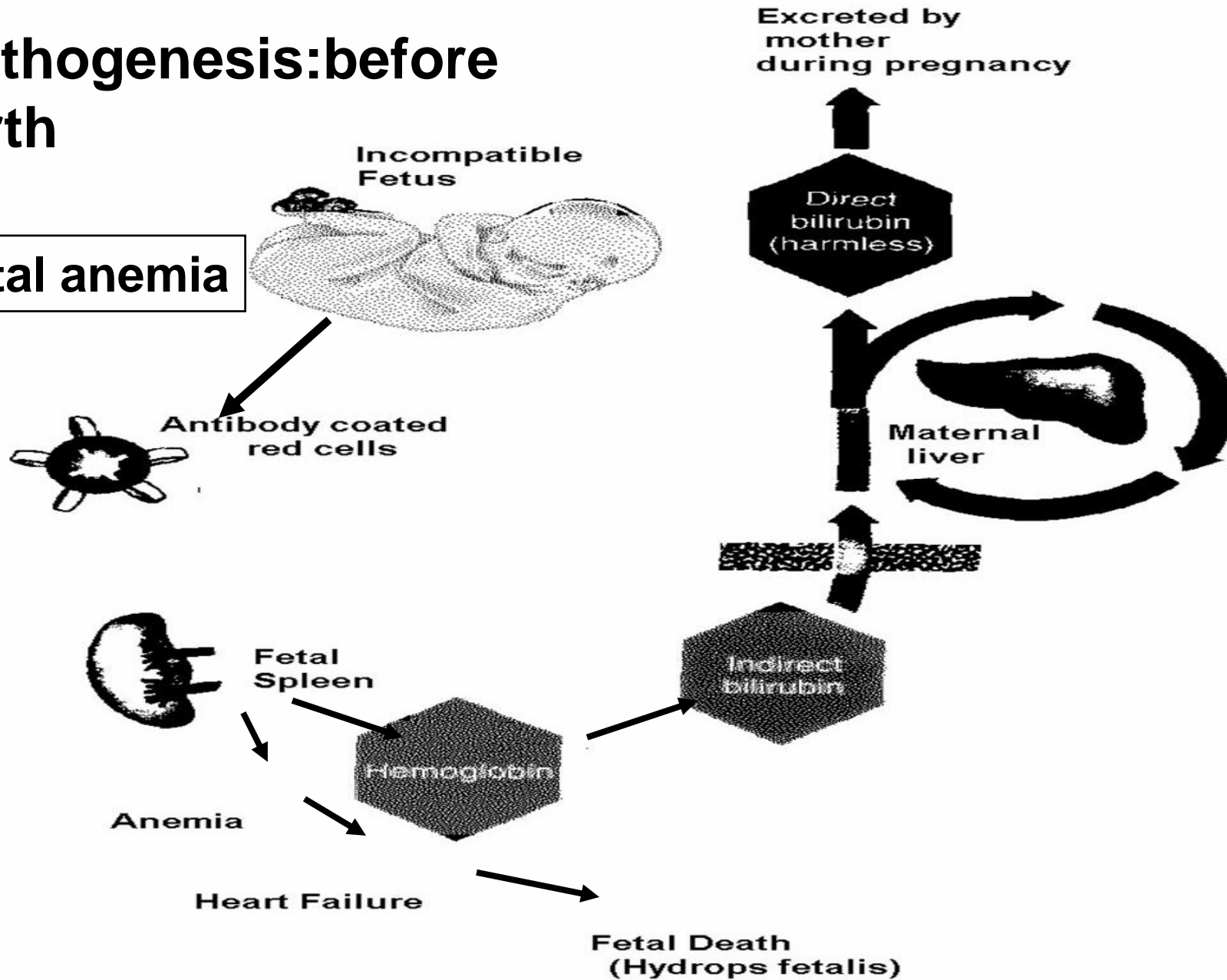
Mother: Rh negative and Immunized
Baby: Rh positive



1. Fetal red cells enter maternal circulation at birth.
2. Red cells are recognized by the mother's immune system.
3. Mother is sensitized and produces antibody.
4. Antibody crosses the placenta and causes HDN.

Pathogenesis: before birth

Fetal anemia



Hydrops Fetalis



Pathogenesis: after

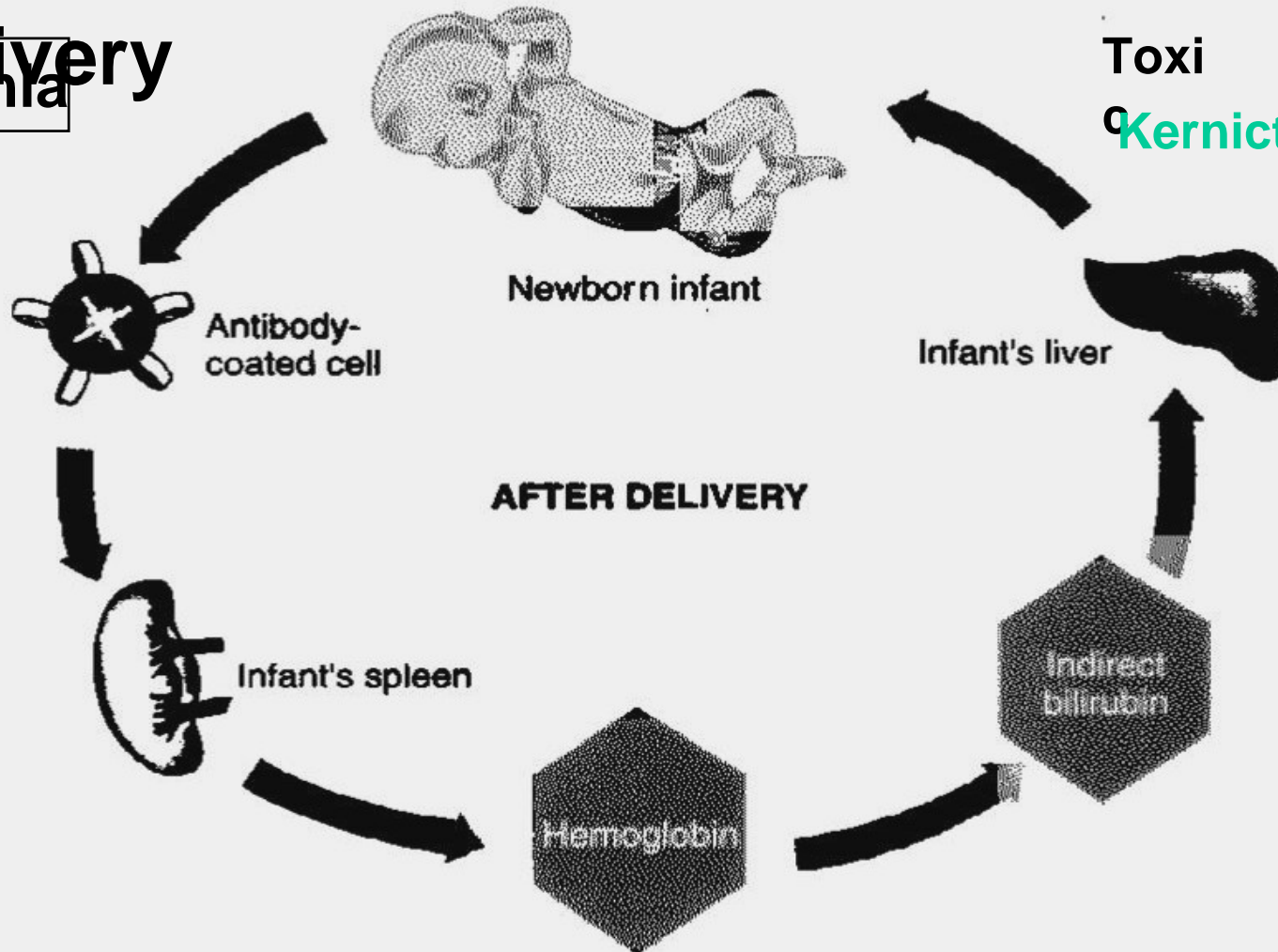
delivery

Anemia

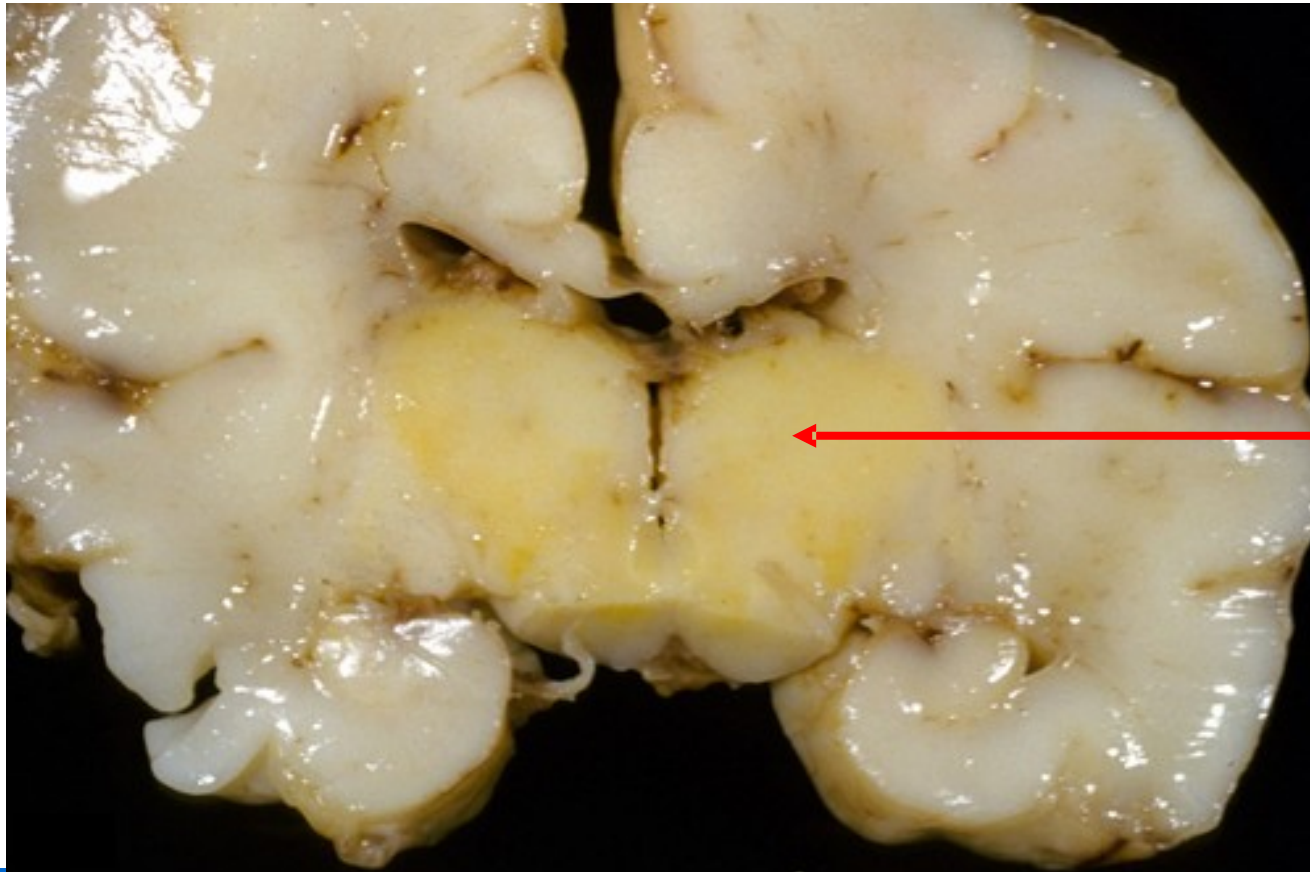
Hyperbilirubinemia

Toxi

Kernicterus



Kernicterus.



Antibodies Involved

- ABO blood
- Rh – anti-D alone or may be accompanied by other Rh antibodies – anti-C, -c, -E or –e.
- “Other” – unexpected immune antibodies other than anti-D – Jk, K, Fy, S, etc.

antibodies implicated most

- Anti - D
- Anti -c
- Anti -K

Management of HDN

- identify 'at risk' pregnancies
- manage alloimmunised mother
- identify and treat anaemic fetus
- identify and treat affected infant
- Identify D neg women for prophylaxis

***BCSH guidelines: Tx Med 2007;17:252-262
Blood grouping and antibody testing in pregnancy***

Testing protocol

All pregnant women, booking (10-16w)
ABO and Rh type Ab screen

If antibody screen negative, repeat at 28
weeks

Anti-D, anti-c, anti-K

- test partner (**hetero** / homozygous)
- obtain transfusion history
- review past obstetric history
- Monitor closely: test 4-weekly to 28w and 2-weekly to delivery
- (special attention anti-K)

Antibody level and HDN risk

| | | |
|-----------|------------|---|
| anti-D | <4 iu/ml | HDN unlikely |
| | 4-15 | moderate risk* |
| | >15 | high risk of hydrops* |
| anti-c | <7.5 iu/ml | continue to monitor |
| | >7.5-20 | moderate risk* |
| | >20 | severe HDN* |
| other Abs | titre<32 | HDN unlikely *refer to specialist unit |

Other IAT-reactive antibodies may cause mild/moderate HDN

- retest once at 28w
 - IAT titre in parallel with booking sample
 - Exclude additional abs
- if titre increasing or >32
 - check outcome of previous pregnancies
 - Doppler MCA
 - repeat serology at **34w**
 - ? early delivery, avoid post dates delivery

Fetus at risk/Assessment of severity

- Past obstetric history
- Maternal antibody level
- Fetal blood sampling / IUT (direct 1981)

fetal DNA PCR genotyping (1993-95)

- MCA Doppler (1995/2000)
- Maternal plasma fetal DNA typing at risk cases (1998-2001)

Past Obstetric history

- Outcome of previous pregnancy gives some indication of expected severity
- Especially when the father is homozygous for RhD

Pre-natal testing of fetal DNA using maternal blood

Non-invasive test (1998-2001)

Fetal DNA can be detected in maternal plasma from the first trimester and DNA increase through pregnancy

Usually performed **>16w:D, E, c**

anti-K, **(20w)**

Non-invasive technique to predict fetal anaemia (1995/2000)

MCA Doppler (1995)

- measure fetal blood flow
peak velocity of systolic
blood in middle cerebral
artery



- detects early fetal anaemia
- Accurate
- non-invasive

*NEJM: Mari et al 2000;342:9-14 Multicentre prospective study
110 cases 15-36 weeks gestation reference range*

Kell Blood Group System and their Frequencies

| | Reactions with Anti- | | Phenotype | Frequency (%) | |
|------------------------------|----------------------|---|-----------|---------------|--------|
| | K | k | | Whites | Blacks |
| (Kell positive Homozygous) | + | 0 | K+K+ | 0.2 | Rare |
| (Kell positive Heterozygous) | + | + | K+k+ | 8.8 | 2 |
| (Kell negative) | 0 | + | k+k+ | 91.0 | 98 |

Anti-K HDN need special attention

Anti-K in pregnancy

Women with anti-K n=168

Partner n=30(K+) n=**138**(K-)*

Among **138*** women, 76 were contacted, all gave transfusion history (**Induced by previous Tx**)

Prevention

Tx all women age <60 with K- blood

Anti-K HDN / HDF

Anaemia associated with low bilirubin reticulocytopenia
Anti-K titre not relevant

a) Suppression of fetal erythropoiesis

anti-K inhibits K⁺ BFUe and CFUe

(Vaughan et al)

b) Immune destruction

Erythroid Progenitors bind by anti-K, removed by macrophages in fetal liver cells

(Daniels et al Transfusion 2003;43:115-116)

Anti-K HDN/HDF

- Anti-K at booking sample
- Check transfusion history
- Check partner's K type

- if partner K neg, with transfusion history transfusion induced

- Once confirmed that the index partner is the father, repeat at 28w

Anti-K HDN/HDF

- Reported HDN titre 1:32
No direct correlation between antibody titre and severity of HDN
- if partner Kell + check zygosity
- if partner KK, monitor fetus Doppler / refer to fetal medicine unit
- if partner Kk, undertaken Antenatal maternal sample K typing (>20wks)

Women with rising antibody titre, other than

Anti-D,c,K: **Anti-C,E,Fy^a,Jk^a**

Should they be delivered early?

- previous outcome
- scan findings
- MCA doppler findings
- consider if severity of HDN will be > risk of pre-maturity
- avoid post dates delivery

Diagnosis of HDN at delivery

- If maternal sample contains IAT reactive Ab
- A cord DAT must be done ASAP at delivery
- If DAT is +ve, check Hb and bilirubin; eluate studies to diagnose HDN
- if DAT is -ve, no risk of HDN (except ABO)

ABO HDN

Caucasians : ABO HDN; Hydrops rare

- Presents as mild HDN
- Weak expression of A,B antigens in fetus even not fully developed at birth
- A,B antigens present on other tissues /body fluid

Asians/Arabs/black people prevalence 2-6 times higher

- Strong expression of A,B antigens
- Parasitic infection high levels of ABO antibodies

ABO HDN



Blood and Transplant

- first/late pregnancy (O mother and A/B baby)
- neonatal jaundice is first sign and prompts investigation
- maternal IgG anti-ABO titre not predictive

If previous history of ABO HDN

- hospital delivery
- cord ABO gp, DAT, bilirubin, Hb (baseline)
- DAT may be negative in mild /moderate case
- bilirubin peak is later 1-3 days after birth
- do not discharge early/retest later
- community midwife to monitor baby for jaundice/poor feeding etc

RhD immunogenicity

- D most immunogenic (50 times > other Rh)
- Concurrent ABO incompatibility protect against RhD immunization
- Primary immunization dose dependant
1ml: 15%; 250ml: 70- 90%
- Secondary: as little as 0.03ml of RhD pos cells

Prevention of anti-D HDN

- selecting D- blood for D- women is standard practice (recently introduced K)
- all pregnant women are D typed and Ab screened at first visit: identifies those eligible for Rh prophylaxis

Anti-D prophylaxis

- 1) Routine post-natal prophylaxis (1969)
 - a) Abortion (1976)
 - b) Antenatal sensitizing events (1981)

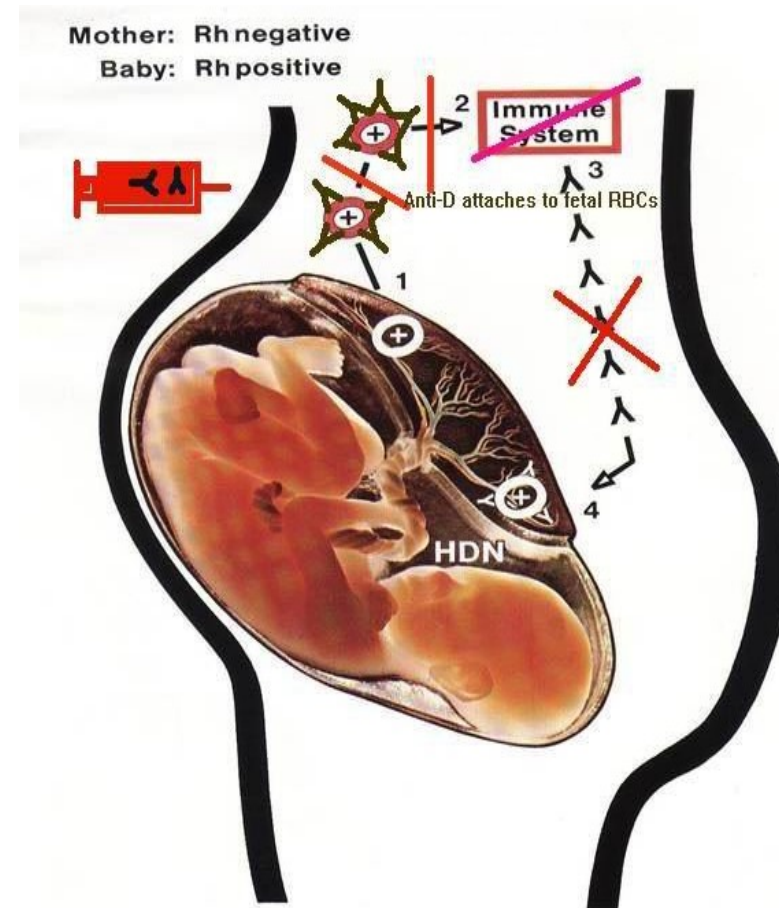
Anti-D prophylaxis programme

- 1) Routine post-natal prophylaxis (1969)
 - a) Abortion (1976)
 - b) Antenatal sensitising events (1981)

- 2) Routine Antenatal Anti-D Prophylaxis
RAADP (2002)

Anti-D prophylaxis

- Not completely understood
- (AMIS) antibody – mediated immune response
- Administered anti-DIg will bind the fetal RhD+ cells
- 1) Antigen deviation
- Macrophages capture/ remove anti-D coated RhD + cells prior to contact with antigen presenting cells



1. Fetal red cells enter maternal circulation at birth.
- ~~2. Red cells are recognized by the mother's immune system.~~
- ~~3. Mother is sensitized and produces antibody.~~
- ~~4. Antibody crosses the placenta and causes HDN.~~

Potential sensitising events

Uterine bleeding

- <12 weeks bleeding completely stopped

No anti-DIg

- Recurrent uterine bleeding <12w heavy bleeding, pain, gestation approaches 12w

(confirmed by ultrasound) anti-D Ig 250iu

- Recurrent bleeding, >12w if bleeding continues
(anti-D Ig, 250iu: 6 weekly intervals)

Abortions

Following abortions (12-20wks)

- Spontaneous abortion >12w
- All therapeutic abortions
- Abortion <12w + interventions
- anti-D Ig 250iu
- Fetus RhD antigen is well developed by 30 - 40 days.

Antenatal sensitizing events

- Recurrent Uterine bleeding >20 weeks gestation
- anti-D 500iu 6 weekly interval
FMH estimation every 2 weekly interval.
if FMH is positive give additional anti-D
- Retested FMH 72hr post dose.

Antenatal sensitising events

- ante-partum hemorrhage
- percutaneous umbilical blood sampling*
- amniocentesis*
- chorionic villus sampling*
- Intrauterine procedures
- external version of the fetus
- closed abdominal injury
- ectopics*, IUD, stillbirth
- abortions

BCSH guidelines: Tx Med 2007;17:252-262

Blood grouping and antibody testing in pregnancy

Events likely to associate with large FMH

- Traumatic deliveries (including CS)
- Manual removal of placenta
- Stillbirths, IU Death
- Ab trauma (third trimester)
- twin pregnancies (at delivery)
- unexplained hydrops fetalis

Danger of lack of information re: anti-D administration

- Misinterpretation that it is immune anti-D and may deprive non-immunized women anti-D prophylaxis

If anti-D 'missed'

- worth giving up to 10 days later
- consider IV anti-D

- More formal assessments needed for failure of RAADP?(SHOT)
- Fetal blood genotyping in maternal circulation
(early booking 16/20 wks antenatal samples Bristol IBGRL) as 60% D neg women will carry D pos fetus

“Other” Hemolytic Disease

- Uncommon, occurs in ~0.8% of pregnant women.
- Immune alloantibodies usually due to anti-E, -c, -Kell, -Kidd or -Duffy.
- Anti-K
 - disease ranges from mild to severe
 - over half of the cases are caused by multiple blood transfusions
 - *is the second most common form of severe HDN*
- Anti-M very rare

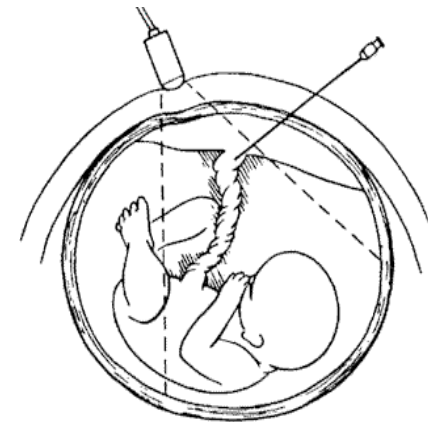
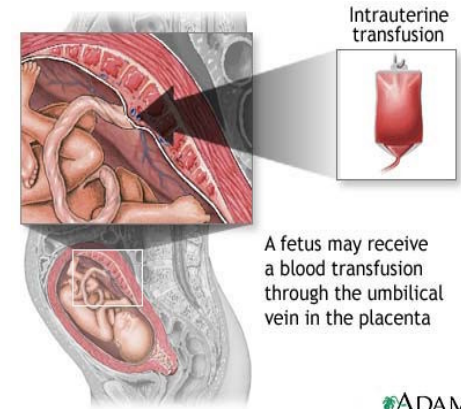
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Intrauterine Transfusion

- The risk of these procedures is now largely dependent on the prior condition of the fetus and the gestational age at which transfusion is commenced.



Treatment options

- Intrauterine Transfusions-severe HDN
- Phototherapy- mild HDN
- Exchange Transfusions- if other parameters indicate it.

Treatment of Mild HDN

- Phototherapy is the treatment of choice.
- Phototherapy process slowly decomposes/converts bilirubin into a nontoxic isomer, ***photobilirubin***, which is transported in the plasma to the liver.
- HDN is judged to be clinically significant (phototherapy treatment) if the peak bilirubin level reaches 12 mg/dL or more.

Phototherapy



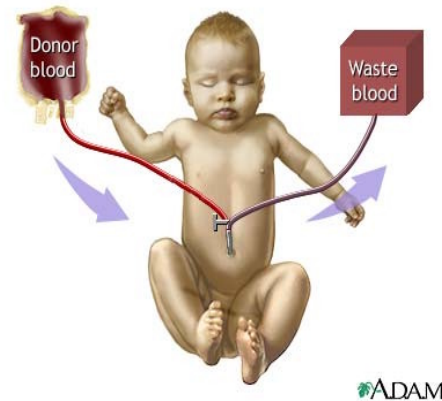
- The therapy uses a blue light (420-470 nm) that converts bilirubin so that it can be excreted in the urine and feces.
- Soft eye shields are placed on the baby to protect their eyes from damage that may lead to retinopathy due to the bili lights.

Phototherapy



- Lightweight, fiber-optic pad delivers up to 45 microwatts of therapeutic light for the treatment of jaundice while allowing the infant to be swaddled, held and cared for by parents and hospital staff.
- Compact unit is ideal for hospital and homecare.

Exchange Transfusion



- Full-term infants rarely require an exchange transfusion if intense phototherapy is initiated in a timely manner.
- It should be considered if the total serum bilirubin level is approaching 20 mg/dL and continues to rise despite intense in-hospital phototherapy.
- The procedure carries a *mortality rate of approximately 1%* and there may be substantial morbidity

Summary

- HDN can vary in severity.
- More than 40 antigens have been identified as causing HDN.
- Laboratory testing key to diagnosing and monitoring- great care to be taken when interpreting ABO/D typing on affected infants.
- Therapy dependent on severity: phototherapy alone or with transfusion.