The therapy and prevention of the haemolytic disease of the fetus and newborn (HDFN)
Transfusion of the newborn and infant

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Immunhematological screening of pregnant women

- Regulated by:
  - Decree 26/2014 (IV.8) EMMI
  - Hungarian Transfusion Regulations
- blood group serological screening of pregnant women as part of:
  - ABO blood typing
  - RhD blood typing
  - Antibody screening (LISS/AGT and enzyme medium) - if positive: identification, titre test, paternal sample
  - Direct Antiglobulin Test (DAT)

The aim

- recognising pregnancy at risk of haemolytic disease of the foetus and newborn (HDFN)
- RhD negative pregnant women must be identified - they have to receive anti-D IgG prophylaxis
- screening for irregular antibodies in the serum during pregnancy
- Transfusion order - ensure compatible blood product, be prepared for possible maternal transfusion or blood exchange of the newborn

Dates of the tests

- First trimester (10-16. weeks): every gravida
- Second trimester (around 28 weeks): all RhD negative gravida and RhD positive gravida with positive immunization anamnesis
- Third trimester (32-36. weeks): all gravida
- The blood group serology result is always valid until the next screening

Positive antibody screening in pregnant women

- In the presence of a clinically significant alloantibody (may cause HDFN):
  - determine the concentration/strength of antibodies using titration
  - there is no correlation between titre and the severity of fetal damage, but significant changes in titre require closer follow-up
  - pregnancy with a titre of 1/32 should be monitored closely

Positive antibody screening in pregnant women

- In the case of alloantibody, it is important to test the Ig class and IgG subclass of the antibody
- IgG1 and/or IgG3 subclasses cause severe fetal or neonatal haemolytic disease

- Autoantibodies do not usually cause severe fetal damage requiring blood exchange, but may mask clinically significant alloantibodies. They may cause fetal harm through maternal anaemia.

Paternal blood sample testing

- It may be helpful to test paternal red blood cells for the antigen to which the maternal alloantibody is produced
  - The fetus could have inherited the specific antigen only from the father (half of the foetus' genetic pool comes from the father and this could be unknown to the mother's immune system)
- If the father does not have the target antigen, no HDFN should be formed
- If the father is heterozygous for the relevant antigen, there is a 50% chance that this antigen is present on the fetus red cells

HDFN

- Maternal antibody production is due to previous immunization
- Conditions with potential immunization:
  - Foetomaternal transfusion - fetal RBC's are unknown
  - Termination of previous pregnancy (childbirth, abortion) - immune response against fetal red cell antigen
  - Previous transfusions - the donor RBCs are triggered the immune system

HDFN

- 0.1 ml of fetal blood is enough for maternal immunisation
- The IgG class antibody crosses the placenta and binds to the corresponding fetal red cell antigen → the newborn will be DAT positive!
- Fetal red blood cells are destroyed:
  - Anaemia → hypoxia → icterus → hydrops
  - from anaemia to stillbirth

HDFN

- Mechanism:
  - IgG-type antibodies cross through the placenta and sensitize fetal red blood cells (antigen+antibody binding) which break down in the reticulo-endothelial system
  - Part of the freed haemoglobin is passed through the placenta and excreted in the mother's liver as bilirubin
  - Fetal spleen and liver are enlarged, partly due to increased red cell destruction and partly due to increased haematopoiesis
    - During fetal life, since bones and thus the bone marrow develop later, the liver functions as the main haematopoetic organ

HDFN

- The degradation of RBCs continues in the newborn, bilirubin is transported to the liver, but the immature liver is unable to conjugate the bilirubin, so elimination is slow
- Non-conjugated bilirubin is toxic and may accumulate in the central nervous system, resulting in kernicterus
- The associated severe anaemia can risk the life of the newborn in the first 7-10 days
- It is important to monitor the increase of Bi and the decrease of Hgb
- Increased destruction of maternal antibody-coated RBCs indicates transfusion in the first 6 weeks

Kernicterus

- Kernicterus is a bilirubin-induced brain dysfunction
  - The blood-brain barrier is not fully functional in neonates and therefore bilirubin is able to cross the barrier
  - Hyperbilirubinemia may cause bilirubin to accumulate in the grey matter of the central nervous system, potentially causing irreversible neurological damage
  - Depending on the level of exposure, the effects range from clinically unnoticeable to severe brain damage and even death

HDFN

- Fetal RBCs can trigger immunization by entering the mother's circulation during the first pregnancy, but usually no fetal anaemia is developed
- Maternal antibody crossing to the fetus is minimal in the first trimester, increases exponentially in the third trimester
  - antibody appearing after 28 weeks does not usually cause severe HDFN
- During the following pregnancy, antibodies will cause HDFN if the fetus carries the target antigen

HDFN

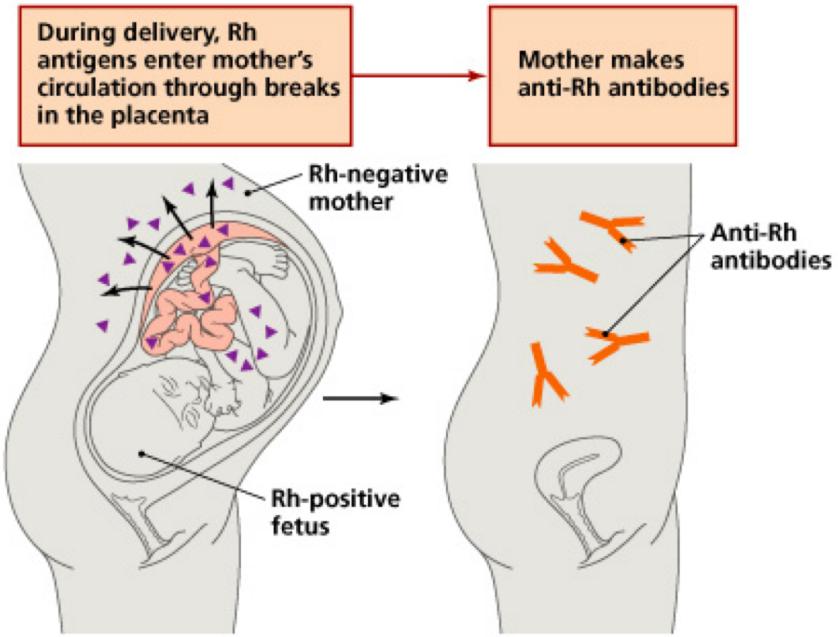
- ABO incompatibility between mother and newborn
- Alloantibody of Rh system:
  - **anti-D**, **anti-c**, anti-e, anti-E, anti-C
- Other alloantibodies of blood group system:
  - **anti-K** (Kell)
  - anti-Fya, anti-Jka, anti-M,N,S,s, etc.

ABO incompatibility

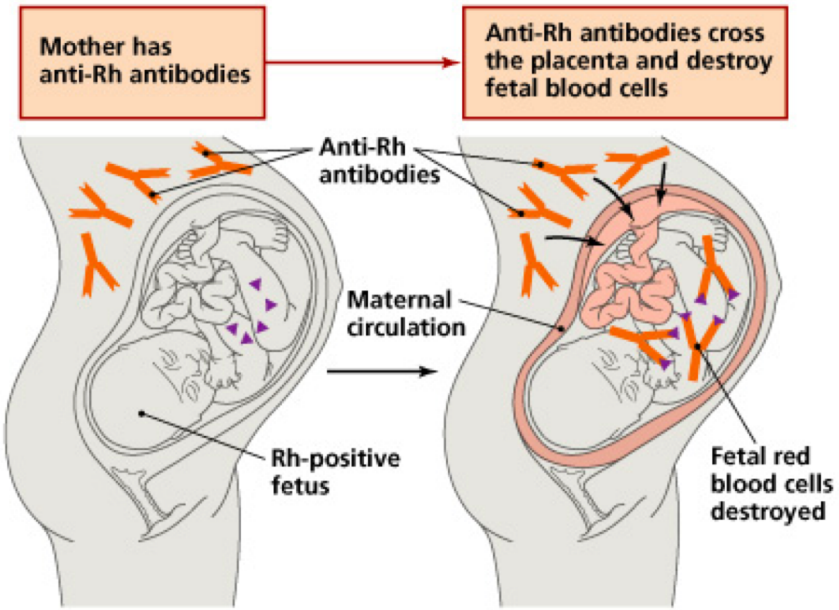
- Most often found in group A or B neonates from mother with group 0 phenotype
- More anti-A, anti-B antibodies are present in group 0 individuals with a small amount of IgG class antibodies that cross the placenta
- Usually has a mild presentation, can develop in the first pregnancy and cause mild DAT positivity in the newborn
- Postnatal icterus can usually be treated with phototherapy, rarely requires blood exchange

HDFN caused by anti-D

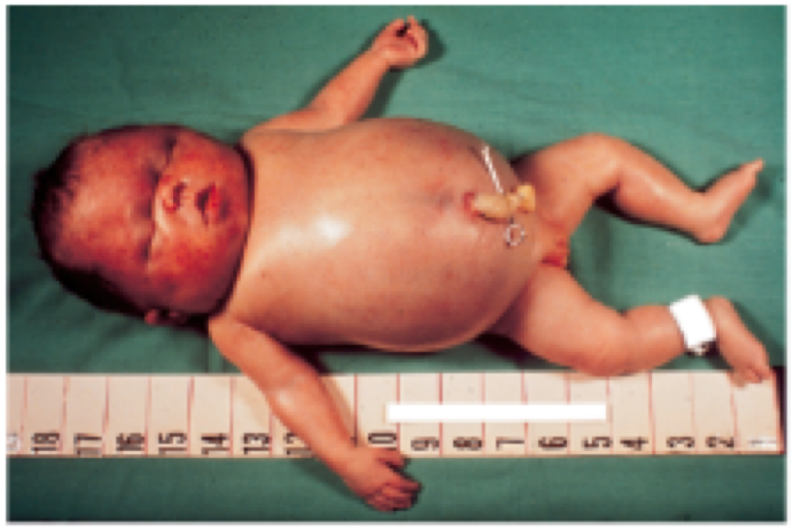
- RhD negative (or weak D variant) pregnant women with RhD positive fetus are likely to produce anti-D antibodies
- Anti-D is always IgG type that crosses the placenta and can cause severe fetal haemolytic disease
  - associated with severe jaundice, miscarriage, stillbirth, child birth with hydrops
- It usually presents during the second pregnancy



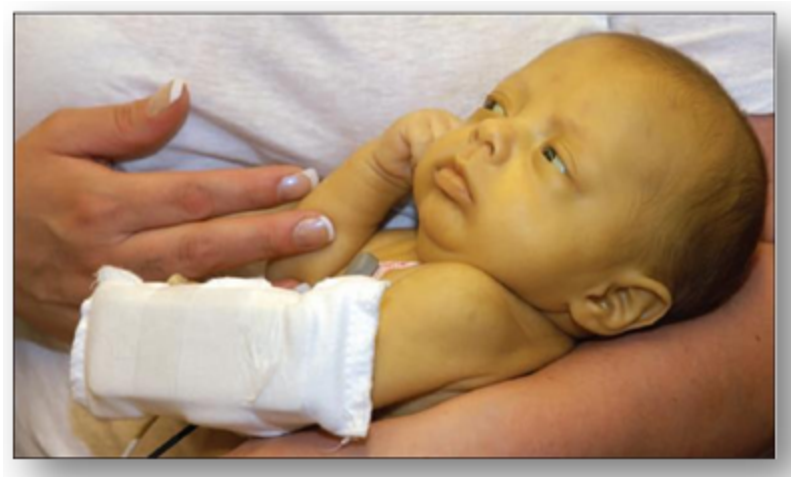
(a) First pregnancy



(b) Subsequent pregnancy



Hydrops fetalis



Jaundice

The chance of immunization in RhD negative gravida

- if ABO incompatibility is present between RhD negative mother and her RhD positive fetus, the chance of immunization is < 2%
  - maternal anti-A or anti-B destroys fetal red blood cells in the circulation before they are recognised by the mother's immune cells
  - e.g.: O RhD neg gravida has A or B RhD pos fetus
- If ABO compatibility is between mother and fetus, the chance of immunization is 7-8%
- ABO incompatibility does not protect from secondary immunization

HDFN caused by anti-D

- The anti-D titre is based on experience:
  - 1/16: requires increased monitoring
  - 1/32: can cause severe harm (but not necessarily)
- The umbilical cord sample of the newborn will be DAT positive: from weak to strong (+ → ++++)
- Newborn's red cells are covered with maternal anti-D antibody, so the phenotype of the neonate may be mistakenly shown to be RhD negative

Anti-D IgG prophylaxis

- RhD-negative gravid women should receive anti-D IgG prophylaxis within 72 hours of following potentially sensitising events:
  - Invasive intervention during pregnancy, hemorrhage/injury
  - Following delivery, postpartum
  - 50 µg up to the 12th week and after then 300 µg
- Variant D mother is considered RhD negative for immunization aspects
- D variant newborn is considered RhD positive for immunisation aspects

Anti-D IgG prophylaxis

- Mechanism: the injected anti-D binds to the D antigen of the fetal RBCs that have entered the mother's circulation, so they are removed from the circulation before the maternal immune system is activated
- 300 µg of anti-D IgG is enough to cover 15 ml of fetal RBC
  - with a normal delivery about 4-5 ml of fetal blood cells being passed to the mother's circulation
- Increased dose (2x300 µg): sectio, manual placental abruption, stillbirth, twin birth, unexplained hydrops, >30 ml of fetal RBC are passed

Anti-D IgG prophylaxis

- Half-life of injected anti-D is 18-21 days
- Prophylaxis in pregnancy results passive antibody exposure, that can be detected by antibody screening (for about 4 months after exposure)
- On the blood group test request form, it must be noted when the anti-D IgG prophylaxis was given

Antenatal anti-D IgG prophylaxis

- Routine antenatal anti-D Ig prophylaxis (RAADP)
- UK, USA, Canada:
  - anti-D IgG is given rutinly to pregnant women before delivery (28th and 30-32th weeks)
  - Prevalence of anti-D alloantibody is less than 1%
- Not used in Hungary but gravid women who have received antenatal prophylaxis can give birth here

HDFN caused by anti-c

- Causes the most severe fetal harm after anti-D
- C homozygous mothers can formed if have a fetus with c phenotype
- The newborn will be DAT positive because their RBCs are covered with maternal anti-c antibodies

HDFN caused by anti-Kell

- Can also cause serious fetal damage
- Develops in the Kell positive fetus of mothers with Kell negative
- Jaundice of the newborn may be mild because anti-K binds to Kell positive at the level of progenitor cells
- Severe anaemia of the newborn

Antibodies that do not cause HDFN

- Lewis, I, Cartwright ~ do not develop until the time of birth
- Usually cold type antibodies (IgM) - I, P1, N, Cromer, Ch/Rg, etc.
- Maternal autoantibodies

Handling a pregnancy with a high risk of HDFN

- If anti-D, anti-c or anti-K alloantibodies are detected during pregnancy screening, the pregnant woman should be recalled for follow-up tests every month until the 28th week and every two weeks from the 28th week
- Antibody identification and titration should be performed at each visit
- Any titre change should be reported to the gynaecologist, antenatal nurse
  - (closer monitoring with US, amniocentesis if necessary, Doppler examination, programmed induction of labour if needed)

Intrauterine transfusion

- If hydrops symptoms are detected during the ultrasound examination, intrauterine transfusion is a possible treatment for fetal anaemia
  - from 22-24 weeks (18 weeks at the earliest)
  - repeated every 2-4 weeks
- 3-5 day-old red cell concenrtate, Htk 70-75%, filtered, washed, irradiated less than 24 hours
- As the fetus' blood group is unknown, we supply a blood type O, RhD negative, Kell negative red cell concentrate that is selected to the mother's serum

Blood exchange of the newborn

- Blood exchange is required in 60% of anti-D HDFN and 30% of anti-c HDFN
- In the presence of severe hyperbilirubinaemia and/or anaemia
- Consultation with a transfusion specialist should always be the first step

Blood exchange of the newborn

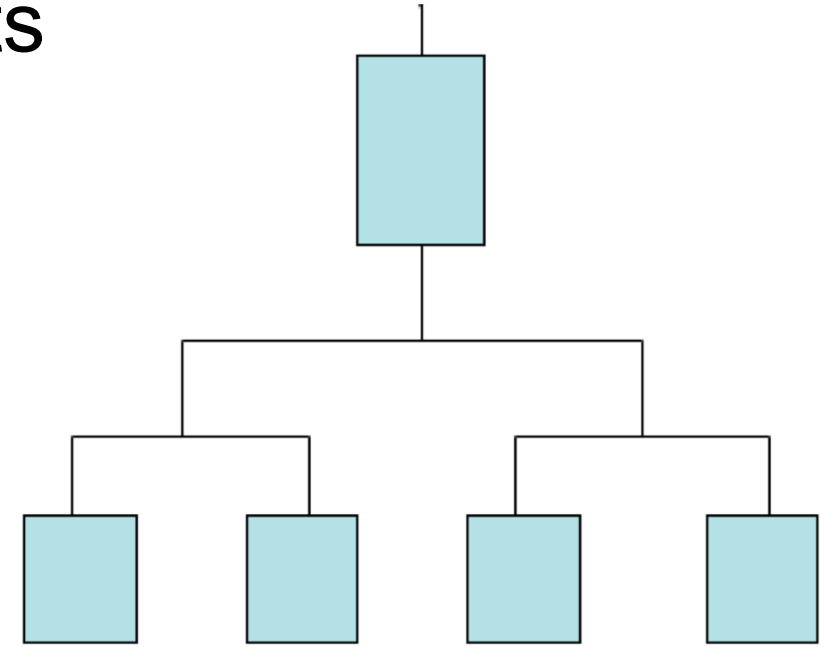
- Blood product characteristics:
  - the minimum volume should be 2-2.5 times the total blood volume of the newborn.
  - be compatible with AB0, RhD characteristics of mother and newborn
  - selected to the mother's serum
  - not older than 5 days, maximum 7 days
  - leukocyte-depleted
  - with haematocrit set at approximately 50%
  - possibly irradiated
- blood product must be warmed to 37 °C before transfusion

Prevention of HDFN

- Anti-D prophylaxis
- Prevent immunization of RhD negative women in reproductive age and RhD negative female children:
  - RhD negative red cell and platelet concentrate can be transfused only
  - Supply of K negative products
  - C homozygous individuals should not be given c positive red cell concentrate

Neonatal transfusion

- Split units of a normal red cell concentrate
- 1 unit RCC is divided into 4 split units in a closed system
- 50-50 ml filtered, irradiated products
- 4 transfusions can be performed within 15 days



Neonatal transfusion

- We also have split FFP products
- Platelet concentrate is reduced in volume (approximately 25 ml) for neonatal use.

thank you