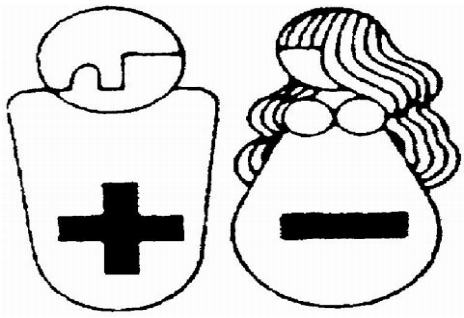
RH ISOIMMUNIZATION



429 OB/GYN team

Resources: Hacker and Moore's, Sakala, dr. Ghadeer's Slides and 428 ob/gyn team

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DEFINITIONS

ISOIMMUNIZATION

- The condition that occurs when the mother's immune system produces anti-bodies directed against foreign RBC surface antigens, often those of her fetus.
- The most common antigens involved are those of the rhesus blood group system, but any RBC antigens may be involved.

RH ISOIMMUNZATION

- An immunological disorder that is one of the causes of hemolytic disease of the newborn (HDN).
- It typically occurs only in some second or subsequent pregnancies of Rh negative women where the fetus's father is Rh positive, leading to a Rh+ pregnancy.
- If a woman has a history of Fetal hydrops with a previous pregnancy, the risk for having hydrops with a subsequent pregnancy is about 90%.

BLOOD GROUP ANTIGENS

The Rh complex, in the blood, is made up of:

- **Antigens:** including C, D, E, c, e and other variants such as D^u antigen.
- If the person lacks the D antigen on RBCs surface, he/she will be Rh-negative while a person with the D antigen is Rh-positive.

'D' ANTIGEN

It is the main rhesus blood group antigen in isoimmunization, with the following genetical characteristics:

- The locus is on the short arm of chromosome 1.
- The zygosity of D antigen-positive men is as follows:
  - 60% are heterozygous (Dd); might have a Rh- offspring
  - 40% are homozygous (DD); always have a Rh+ offspring

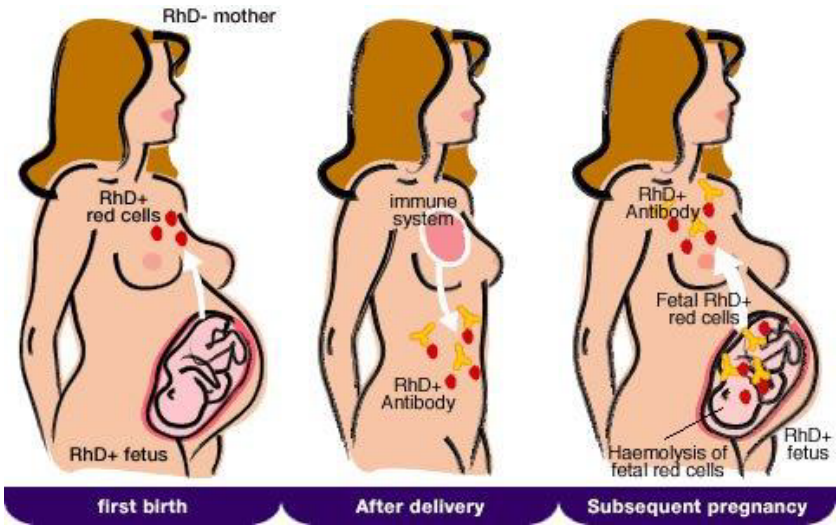
PREVALENCE and INCIDENCE

- Incidence of Rh negativity varies according to race:
  - Basques of France and Spain 30%
  - Caucasian Americans 15%
  - Hispanic Americans 10%
  - African Americans 6%.

- It affects 1 in 250 live births in Europe and North America; it is much less frequent in other parts of the world such as Asia, where the Rh-negative blood group is uncommon.

PATHOPHYSIOLOGY

- Rh isoimmunization can only take place if fetal red cells cross the placental barrier into the maternal circulation.
- During birth, the mother may be exposed to the infant's blood, and this causes the development of antibodies, which may affect the health of subsequent Rh+ pregnancies.
- The risk and severity of *sensitization response* increases with each subsequent pregnancy involving a fetus with Rh-positive blood
- Second pregnancy with an Rh-positive fetus often produces a mildly anemic infant



IMMUNE RESPONSES:

- Primary – initial response to an antigen appears after several weeks and is the production of **IgM**.
- Secondary – when exposed for the 2nd time, a primed, antibody will be produced faster, within a few days and it's **IgG**.
- Generally, the quantity of antigen required to produce a secondary immune response is very much smaller than that required to initiate the primary immune response.
- Two exposures to the Rh antigen are required to produce any significant sensitization, unless the first exposure is massive.

NATURAL HISTORY

- Rhesus antibodies are humoral antibodies or free antibodies
    - IgM – large, unable to cross the placenta
    - IgG – small, to cross the placeta and

- If the fetus has the Rh-antigen, these antibodies will coat the fetal RBCs and cause hemolysis.
- The antibody attaches itself to Rh positive red cells leading to haemolytic anaemia (causes a transfusion reaction; the mother's body reacts to the fetus' blood as if it were an incompatible blood transfusion and lyse it).

OUTCOME

- > If the hemolysis is ***mild*** → the fetus can compensate by increasing the rate of erythropoiesis and may have a mild anemia with reticulocytosis (increase in immature red blood cells).
- > If the hemolysis ***moderate*** or ***severe*** → the fetus may have a more marked anemia and erythroblastosis (nucleated red blood cells or erythroblastosis fetalis).
- > In ***very severe cases*** → HDN, hydrops fetalis, or stillbirth
- The risk and severity of sensitization response increases with each subsequent pregnancy involving a fetus with Rh-positive blood.
- Second pregnancy with an Rh-positive fetus often produces a mildly anemic infant

CAUSES OF FETOMATERNAL HEMORRHAGE:

Most of the bleeds occur in the last trimester when the placenta is degenerating and the barrier may become a little more pervious. The most common causes:

1. After spontaneous or induced abortion (especially after 14 weeks)
2. Trauma
3. Invasive obstetric procedures as amniocentesis, Chorionic villous sampling or ectopic pregnancy
4. Normal delivery (The placenta is subjected to maximal trauma during delivery).
5. Rh-negative female receives an Rh-positive
6. Blood transfusion.
7. APH
8. Threatened miscarriage
9. Toxemia
10. Hypertension
11. External cephalic version

MANAGEMENT

PREVENTION and ANTENATAL CARE

- A blood sample from every pregnant woman should be sent at first prenatal visit for determination of the ABO blood group, Rh type and for antibody screening.
- In case of Rh-negative results, ***Maternal Antibody titers*** should be made to detect whether she was sensitized or not (if negative, the test should be repeated at 28 and 35 weeks).
- Rh immune globulin Rh_0-GAM (also called Anti-D IgG) diminishes the availability of the Rh antigen to the maternal immune system to prevent Rh isoimmunization (the mechanism is not well understood)

ABO COMPATIBLE

When the mother and the baby have the same blood group:

- All rhesus-negative unsensitized women who **have any risk factor** (risk factor for fetomaternal hemorrhage or any antepartum event) are given anti-D IgG.
- All rhesus-negative unsensitized women are given anti-D IgG **at 28 weeks gestation** and repeated **at 34 weeks gestation**
- All rhesus-negative unsensitized women are given anti-D IgG **after delivery within 72 hours**
- If the mother has been sensitized previously (determined by elevated level of maternal Rh antibodies), administration of Rh IgG has **no** value

ANTI-D FAILURE RATE

About 1% of Rh-ve women become immunized after D-positive pregnancies despite treatment with Rh immunoglobulin.

- Those already primed, even though overt antibody is undetectable by present techniques.
- Large FMH's before delivery e.g. epileptic or eclamptic patients.
- Extreme sensitivity to the D-antigen: thus small bleeds will produce primary response.
- Large FMHs after delivery more than the amount that can be taken care of by standard dose of immunoglobulin.
- Failure to give the immunoglobulin – patients who slip through the net.

ABO INCOMPATIBLE

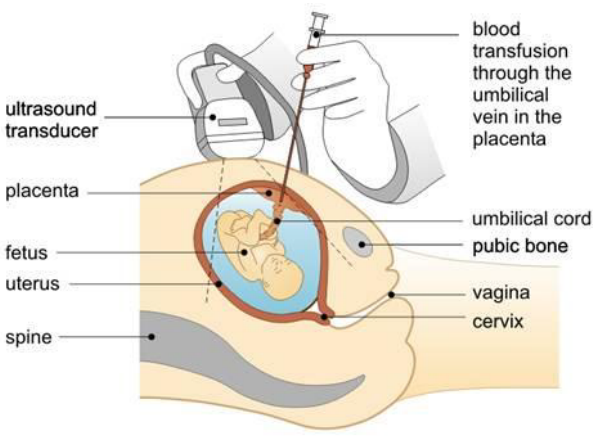
- When the mother and the baby are ABO incompatible such as an O mother and an A or B baby, any fetal red cell (Group A or B) entering the maternal circulation (Group O) is destroyed in an exactly similar way to that occurring in an ABO incompatible blood transfusion
- Anti-A and anti-B antibodies are present in the maternal circulation naturally, and hence do not require prior sensitization in order to be produced
- This means that ABO incompatibility may occur in a first pregnancy.
- Those antibodies should be screened by AAT or coombs test:
    - If negative → no fetal risk.
    - If positive < 1:8, it's insignificant and HDN is negligible.
    - If positive > 1:8, it's significant and fetal evaluation for anemia should be carried out

- Most of cases ABO incompatibility causes mild hemolytic disease of the babyà no screening for ABO hemolytic disease
- Diagnosis is usually made by investigation of a newborn baby who has developed jaundice during the first day of life
- Treatment: Neonatal jaundice caused by ABO HDN is usually successfully treated with phototherapy and in case of severe hemolytic anemia à the management as Rhesus isoimmunization.

IN SENSITIZED WOMEN

Women with positive antibodies should undergo the following:

1. **Serial Ultrasound:**
   To detect hydrops fetalis (skin edema, ascites, pleural or pericardial effusions cardiomegaly and an edematous placenta)
2. **Serial Doppler examinations of middle cerebral artery and umbilical artery:**
   For detection of increased blood flow velocities (sign of anemia)
3. **Quantitative analysis of maternal anti-RhD antibodies:**
   High levels are reflected of fetal Rh disease
4. **Amniocentesis**
   For the level of bilirubin to assess the severity of hemolysis
   (Amniotic fluid bilirubin concentration can be quantified by spectrophotometry by assessing the change in optical density at 450nm).
5. **CTG**
   A sinusoidal pattern with the loss of normal baseline variability of the CTG is highly suggestive of severe anemia.
6. **Intrauterine Transfusion**
   Transfusing the fetus with Fresh group O, Rh negative packed RBCs that underwent screening. It increases the overall surviving rate to about 85%, but has the following complications:
   - >Premature labor
   - >Pre-labor ruptured membrane
   - >Fetal hemorrhage
   - >Fetal bradycardia
   - >Failure to obtain a sample
   - >Increase in maternal isoimmunization by inducing fetomaternal hemorrhage



DELIVERY DATES

- Severe may be associated with hydrops fetalis (ZONE III) → managed by blood transfusion into the fetal umbilical vein until 32 weeks then immediate delivery
- Moderate to mild (ZONE II) → the delivery is at 35 weeks to term
- Mild or normal (ZONE I) → delivered at term

POSTNATALLY (Postnatal emergency care)

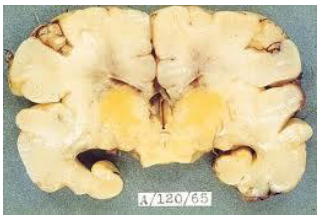
Investigations

The blood of the umbilical cord is examined for the following:

1. ABO group and Rh typing
2. Hematocrit and Hemoglobin
3. Serum bilirubin analysis
4. Blood smear (to show erythroblasts and reticulocytes count)
5. Perform direct Coomb test.

Complications

1. Hydrops fetalis
2. Stillbirth
3. Hepatosplenomegaly
4. Neonatal Kernicterus (The CNS is damaged due to high bilirubin levels; one of the leading cause of cerebral palsy before the widespread use of Rh-immunization prevention)
5. Severe anemia



Management

1. Early exchange transfusion, necessary when:
   - Elevated serum bilirubin
   - Low hematocrit
   - Elevated reticulocyte count
2. Emergent exchange transfusion, ALWAYS performed in the following:
   - Hydorps Fetalis (due to congestive failure and intrauterine fetal death)
   - Erythroblastosis fetalis
   - Neonatal Kernicterus
3. Phototherapy, in mild cases, to treat neonatal jaundice.