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Rhesus Isoimmunization

Objectives:

- Describe the pathophysiology and diagnosis of alloimmunization
- Describe the use of immunoglobulin prophylaxis during pregnancy for the prevention of alloimmunization
- Discuss the management of a patient with Rh-D sensitization in pregnancy

Done by : Ali Alzahrani
Revised by: Qusay Ajlan

Introduction

Definition:

- When a pregnant woman develops antibodies to foreign RBCs of her current or previous fetus. A significant sensitization requires two exposures to the Rh antigen, unless the first one was strong enough.

Mechanisms:

1. Undetected placental leak
2. Grandmother" theory.

Pathophysiology:

- The initial response to exposure to Rh antigen is the production of immunoglobulin M (IgM) antibodies for a short period of time, followed by the production of IgG antibodies that are capable of crossing the placenta. If the fetus has the Rh antigen, these antibodies will coat the fetal red blood cells and cause hemolysis.

Incidence:

- Although transplacental hemorrhage is very common, the incidence of Rh immunization within 6 months of the delivery of the first Rh-positive, ABO-compatible infant is only about **8%**. In addition, the incidence of sensitization with the development of a secondary immune response before the next Rh-positive pregnancy is **8%**. The risk for Rh sensitization following an ABO-incompatible, Rh-positive pregnancy is only about 2%.
- The incidence of immunization following spontaneous abortion is 3.5%, whereas that following induced abortion is 5.5%.
- The risk for immunization following ectopic pregnancy is about 1%.

Risk factors:

- Whenever the fetal cells enter the maternal circulation (feto-maternal hemorrhage) or if she is transfused with mismatched blood.

Protective factors:

- ABO incompatibility.

Requirements (all must be present).

1- Mother must be **antigen negative**

2- Baby must be antigen positive. (So father is **+**).

3- Adequate fetal RBCs must cross over into the maternal circulation

4- Antibodies associated with Hemolytic disease of the newborn (Erythroblastosis fetalis)

5- A significant titer of maternal antibodies must be present to cross over the fetus. (>1:16)

Kaplan→ >1:8, Hacker→ >1:16

Detecting Fetomaternal/Transplacental Hemorrhage

- The **Kleihauer-Betke test** quantitates the volume of fetal RBCs in the maternal circulation by differential staining of fetal and maternal RBCs on a peripheral smear. This can assess whether more than one vial of RhoGAM needs to be given when large volumes of fetal–maternal bleed may occur (e.g., abruptio placentae).

- It is dependent on the fact that adult hemoglobin is more readily eluted through the cell membrane in the presence of acid than is fetal hemoglobin (HbF).

$$\frac{\text{\# of fetal cells counted}}{\text{\# of maternal cells counted}} = \frac{\text{Estimated fetal blood volume (mL)}}{\text{Estimated maternal blood volume (mL)}}$$

- **Rosette test** is a qualitative screening test for detecting significant feto-maternal hemorrhage (>10 mL).

Techniques to Evaluate Fetal Rh Status

- Amniocentesis
- Free fetal DNA in maternal serum
- U/S (we may see hydrops*)
- MCA doppler (most valuable to detect fetal anemia)
- Amniotic fluid spectrophotometry (best to estimate fetal bilirubin concentration)**
- Liley chart or modified Liley chart (Queenan chart)
- Percutaneous umbilical blood sampling (PUBS) → we can measure fetal Hb, Hct, blood gases, pH, and bilirubin levels.

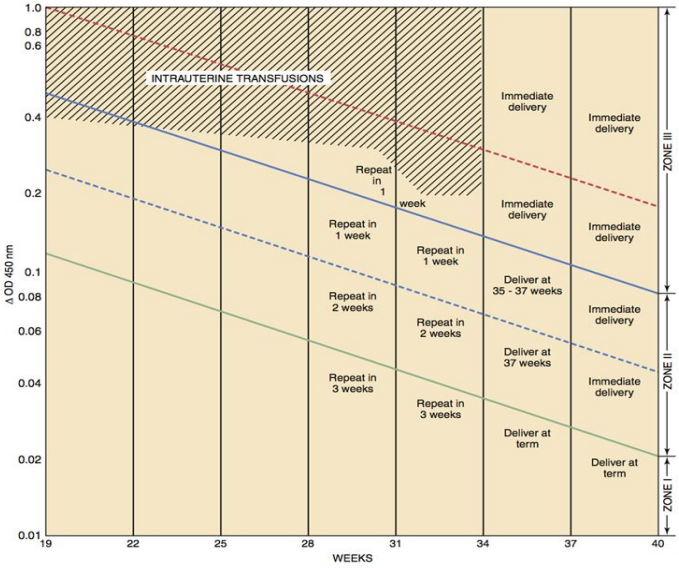


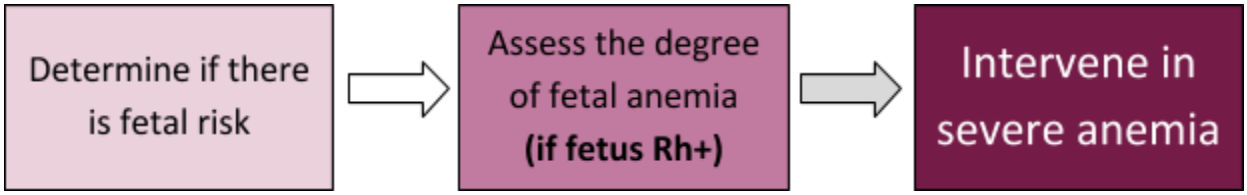
FIGURE 15-2 Modified Liley chart used to determine the appropriate management of the patient with isoimmunization. The optical density at a wavelength of 450-nm (ΔOD 450-nm) level in the amniotic fluid at a given weeks' gestation determines whether fetal transfusion or delivery is advisable.

*Both the placenta and the fetal liver are enlarged with hydrops. Fetal hydrops is easily diagnosed by the characteristic appearance of one or more of the following: ascites, pleural effusion, pericardial effusion, or skin edema.

**There is an excellent correlation between the amount of biliary pigment in the amniotic fluid and the fetal hematocrit, beginning at 27 weeks' gestation.

- The incidence of fetomaternal hemorrhage with amniocentesis → 8.4-11% per procedure.
- The incidence of fetomaternal hemorrhage with PUBS → as high as 40%.

Management Plan/Approach



Determine whether there is any fetal risk. (Kaplan)

- **Fetal risk is present:**

1. Atypical antibodies are detected in the mother's circulation.
2. Antibodies are associated with HDN. Hemolytic disease of the newborn
3. Antibodies are present at a significant titer (>1:8). (1:16) in hacker
4. The father of the baby (FOB) is RBC antigen positive.

    - Fetal blood type may be determined by amniocentesis or percutaneous umbilical blood sampling (PUBS). If the fetus is RBC antigen negative, there is no fetal risk.

- **No fetal risk is present**:
    1. The AAT is negative.
    2. Antibodies are present but are **NOT** associated with HDN.
    3. Antibody titer is <1:8. (1:16)
    4. The father of baby is RBC antigen negative.

- **Atypical antibody titer** is <1:8 (1:16)→management is conservative. Repeat the titer Monthly (2 to 4 weeks) as long as it remains <1:8.

- **Assess the degree of fetal if the fetus is RBC antigen positive or if fetal blood typing is impossible.** This can be done by serial amniocentesis, PUBS, or ultrasound Doppler.

- Amniotic fluid bilirubin indirectly indicates fetal hemolysis because bilirubin accumulates as a byproduct of RBC lysis. The bilirubin is plotted on a Liley graph.
- PUBS directly measures fetal hematocrit and degree of anemia.
- Ultrasound Doppler—measurement of peak flow velocity of blood through the fetal middle cerebral artery (MCA). As fetal anemia worsens, the peak systolic velocity rises.
- Doppler MCA ultrasound is the **procedure of choice since** it is non-invasive and has a high correlation with fetal anemia.

- **Intervene if there is severe anemia**. This is diagnosed when amniotic fluid bilirubin is in Liley zone III or PUBS shows fetal hematocrit to be ≤25% or MCA flow is elevated.

How to Manage the Baby?

- Intrauterine transfusion (fresh O Rh- blood and packed RBCs, repeat transfusions are scheduled at 1 to 3 week intervals, last transfusion should be between 32 and 34 weeks).
- Intraperitoneal transfusion* (RBCs are absorbed via the diaphragmatic lymphatics, Nonhydroptic fetuses absorption should occur in 7 to 9 days, in hydroptic ones it's variable)
- Maternal Plasmapheresis
- Phenobarbital (Has been shown to induce fetal liver enzyme activity and maturation, this is used 2-3 weeks before delivery)

*Formula for intraperitoneal transfusion:

Volume = [GA (wks) – 20] x10

Timing of delivery:

- Fetuses are evaluated at least twice weekly from 24 to 28 weeks for fetal well-being (NST, modified biophysical profile) and fetal growth.
- Delivery is performed if gestational age is >34 week.
- If delivery is expected to occur before 34 weeks' gestation (or if amniocentesis suggests an immature lung profile), betamethasone should be given at least 48 hours before delivery to enhance fetal pulmonary maturation.

Rho-GAM:

- **Prevention**→ pooled anti-D IgG passive antibodies that are given IM to a pregnant woman when there is significant risk of fetal RBCs passing into her circulation. The passive IgG antibodies attach to the foreign RBC antigens, causing lysis to occur before the maternal lymphocytes become stimulated.

- **Uncomplicated pregnancy**→ Rh-negative woman (initial antibody screen is negative should repeat antibody titer at **28 weeks**' gestation. If still negative→routinely receive an intramuscular injection of 300 µg of RhoGAM prophylactically.

- **Within 72 h of** (delivery of an Rh(D)-positive infant, chorionic villus sampling (CVS), or D&C)→ 300 mcg of RhoGAM will neutralize 15 ml of fetal RBCs or 30 mL of fetal whole blood.

- All pregnant women who are **RhD -ve** and **Anti D -ve** and experience→ **(**spontaneous or induced abortion, ectopic pregnancy, significant vaginal bleeding, abdominal trauma, or external cephalic version**)** should receive 50 to 100 µg before 12 week of gestation and 300 µg after 12 week.

- RhO-GAM is probably not necessary for "complete" molar pregnancy, but necessary for "partial" molar pregnancy.

Irregular Antibodies:

- Kell Antibodies can elicit a strong IgG reaction similar to Rh isoimmunization.
- In Kell isoimmunization, the anemia is due to more of suppression of hematopoiesis rather than hemolysis.
- The predictor of anemia in this case is still the MCA PSV. (Like in Rh)

Important notes all over the lecture:

- Fetus can compensate for mild anemia hat is caused by hemolysis. So we only intervene if severe.
- If a woman has a previous pregnancy with fetal hydrops, there is a 90% chance of it occurring again in the next pregnancy (at the same time or earlier in the pregnancy).
- Only direct measure of fetal anemia is PUBS = Cordocentesis.
- Increasing levels of bilirubin will lead to fetal kernicterus which leads to cerebral palsy.
- In Intrauterine transfusions, the goal is to transfuse fresh group O, Rh- negative packed red blood cells/ Overall survival rate following intrauterine transfusion is about 85%.

Case

- **CASE:** A 32 year-old P1101 woman and her new husband present for prenatal care at 20 weeks gestation. Her past obstetric history is significant for a first child delivered at term following an abruption. Her second child died of complications of prematurity following in utero transfusions for Rh alloimmunization. Her initial prenatal labs this pregnancy indicate her blood type as A negative and an antibody screen positive for anti-D with a titer of 1:256. You discuss any additional evaluation needed, her risks in this pregnancy, and the plan of management with her and her husband.

- **What is Rh alloimmunization and what are the red cell antigens involved?**
  - Occurs when any fetal blood group factor (in this case the Rh antigens) inherited from the father is not possessed by the mother. Antepartum or intrapartum fetal-maternal bleeding may stimulate an immune reaction in the mother.
  - Most cases of Rh alloimmunization causing significant hemolytic disease in the fetus or newborn are the result of D antigen incompatibility

- **What are the risk factors for Rh alloimmunization?**
  - Any clinical situation that could lead to fetal-maternal hemorrhage.
  - **Obstetric procedure:** pregnancy termination, chorionic villus sampling, amniocentesis, external cephalic version.
  - Threatened abortion, ectopic pregnancy, abortion
  - Delivery of an Rh+ neonate to an Rh- mother (cesarean or vaginal delivery)—<u>most common cause of alloimmunization</u>
  - Multifetal gestation/ Abdominal trauma
  - Bleeding placenta previa or abruption / Manual removal of placenta

- Spontaneous fetal-maternal hemorrhage has been detected to 10% of cases of alloimmunization.

- **What is the mechanism for RhoGAM prophylaxis against Rh disease? What is the dose of RhoGAM? What is the recommended schedule for RhoGAM administration?**
  - Exogenous IgG (Rho(D) immune globulin) suppresses the maternal immune response through central inhibition. The Rh D IgG coated fetal RBCs are sequestered in the maternal spleen and these antigen antibody complexes inhibit the primary immune response (B cell transformation to plasma cells) and antigen specific B cell proliferation.
  - 300 micrograms of anti-D immune globulin can prevent Rh D alloimmunization after an exposure to up to 30 mL of Rh D-positive blood or 14 mL of fetal cells.
- In the U.S. for Rh-mothers, the recommended immunoprophylaxis regimen using anti-D immunoglobulin is:
  - 300 mcg dose at 28 week EGA.
  - Second 300 mcg dose should be given if delivery has not occurred within 12 weeks of the initial dose.
  - Within 72 hours after delivery of an Rh+ neonate.
  - After first trimester pregnancy loss, threatened abortion, or elective termination.
  - After invasive antepartum procedures or external cephalic version or trauma.
  - After second or third trimester bleeding.

- **Could this patient's Rh alloimmunization have been prevented? What are the ways in which alloimmunization might be diagnosed? Is there any further blood work that should be obtained before you counsel this patient on her risks in this pregnancy? What are some ultrasound findings that may suggest Rh disease?**
  - Administration of an adequate dose of RhoGAM within approximately 72 hours prevents an active maternal antibody response to the fetal antigens. The extent of fetal to maternal hemorrhage can be estimated using the Kleihauer-Betke test.

  - Maternal antibody screen is recommended at the first prenatal visit, at 28 weeks gestation, at the time of any event in pregnancy associated with possible fetal-maternal hemorrhage, and postpartum. Positive antibody screens should be evaluated for strength of antibody response (titer) and type of antibody. A critical titer that may be associated with fetal hemolytic disease is most often between 1:16 and 1:32.

  - The paternal antigen status for the specific maternal antibody should be assessed to determine if the fetus is at risk. This assessment is accomplished by performing direct genotype testing of the father. If paternal testing is not possible, fetal antigen assessment can be accomplished through genetic analysis of fetal cells obtained through amniocentesis.

  - Ultrasound findings consistent with severe fetal anemia include elevated peak velocity of the middle cerebral artery and evidence of hydrops fetalis (fetal subcutaneous edema, pleural and/or pericardial effusions, and ascites).