Teaching Script: Alloimmunization

Clinical Case Applicability:
Prenatal diagnosis – Fetal hydrops, In utero fetal demise or spontaneous abortion, Antepartum care, Fetal-maternal hemorrhage

Learning Objectives:
1) Describe the role of fetal hematopoiesis and the genetics of common red cell membrane antigens
2) Recognize the clinically relevant red cell antigens associated with alloimmunization
3) Describe the pathogenesis of fetal hemolytic anemia due to alloimmunization
4) Explain how to assess fetal risk and diagnose red cell alloimmunization
5) Summarize the possible mechanism(s) by which Rh-immunoglobulin is thought to prevent future alloimmunization

Clinical Presentation:
Miscarriage (prevention); Third trimester demise of hydropic fetus

When and where does fetal hematopoiesis occur during gestation?
• Stimulated by erythropoietin successively during gestation in the fetal yolk sac, liver, spleen and bone marrow

What is red cell alloimmunization?
• When any fetal blood group factor inherited from the father is not possessed by the mother, antepartum or intrapartum fetal-maternal bleeding may stimulate an immune reaction by the mother (sensitization).

How are mothers sensitized to fetal red cells?
• Transfusion of mismatched blood
• Abortion (spontaneous, threatened, elective, therapeutic), Ectopic pregnancy
• Chorionic villus sampling, Amniocentesis, Percutaneous fetal procedure
• Abdominal trauma, External cephalic version
• Abruption or bleeding previa
• Childbirth, Delivery of the placenta

What is the mechanism of erythroblastosis fetalis?
• Subsequent pregnancy > Maternal IgG antibodies > Cross Placenta > Opsonize fetal RBCs (antibody binds to fetal red cell antigen), which are then phagocytized by macrophages in the fetal spleen.
• Results in varying degrees of hemolytic fetal anemia

What red cell antigens cause fetal hemolytic anemia?
Mild versus severe fetal anemia (“Lewis lives and Kell kills”)
• Rh (D) antigen (C, c, E, e)
• ABO incompatibility
• Lewis antigen
• I antigen
• Kell antigen
• Duffy antigens
• Others

What is the pathogenesis and fetal consequences of red cell alloimmunization?
• Initial immune response depends on amount of fetal-maternal hemorrhage, immunogenicity of the fetal red cell antigens, and the immune response capacity of the mother
• Severity of fetal anemia also dependent on other factors: structure, glycosylation and transport of maternal antibodies, polymorphisms of fetal red cell antibody receptors, functional maturity of the fetal spleen
• Severe anemia > high output fetal cardiac failure > fetal hydrops (skin edema, ascites, pericardial effusion); usually correlates with hematocrit <15% or hemoglobin < 5g/dL

How is Rh (D) alloimmunization diagnosed?
• Indirect Coombs test to determine specific antibody and antibody titer
• If maternal antibody, must determine paternal antigen status to assess risk to fetus
• Previously, if antibody titer >1:16, then amniocentesis to determine AF-deltaOD450 which quantitates AF bilirubin spectrophotometrically in a specimen that has been shielded from light (Liley graph with zones 1-3 correlating with degree of anemia) > guided whether invasive fetal transfusion necessary
• Now, MCA dopplers measure peak velocity which correlates with severity of suspected fetal anemia (Noninvasive!)

What is the pharmacology of Rh immunoglobulin (aka Rhogam) to prevent Rh alloimmunization?
• Manufactured from pooled plasma of women with high Rh (D) IgG titers or sensitized male donors
• 300 mcg dose suppresses immune response to 15 ml fetal D+ red cells or 30 ml whole fetal D+ blood
• Mechanism of action unproven; Possibilities: antibody coats fetal D+ cells causing rapid macrophage clearance; Rh immunoglobulin causes down-regulation of antigen-specific B cells before immune response triggered.

**Figures for Animation:**
1. Fetal Hematopoiesis
2. Sensitization Sequence
   - First Pregnancy
   - Second Pregnancy
3. Sonogram images of hydropic fetus from the de-identified Johns Hopkins Prenatal Diagnostic Center teaching files
   - Severe Anemia
   - High-output fetal cardiac failure
   - Fetal Hydrops
   - Skin edema
   - Ascites
   - Ascites & Pleural Effusion
4. Modified Liley or Queenan curve
5. Rhogam mechanism

**References:**
- Moise, KJ. Overview of Rhesus D alloimmunization in pregnancy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA (2017)
- Moise, KJ. Prevention of Rhesus (D) alloimmunization in pregnancy, In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA (2017)