Rhesus (Rh) Alloimmunization

Background
1. Definition
   - Incompatibility between an Rh negative mother and her Rh positive fetus
     - Mother can develop antibody to fetal blood group factor through exposure to fetal blood antenatally

2. General info
   - Fisher-Race nomenclature for Rh blood group system includes five major (C, c, D, E, e), and many variant antigens expressed on blood products
   - Most cases of Rh alloimmunization result from incompatibility w/D antigen
   - Rh positive - refers to presence of D antigen
   - Rh negative - refers to absence of D antigen on erythrocytes

Pathophysiology
1. Pathology of disease
   - Fetal-to-Maternal hemorrhage
     - Happens spontaneously in most pregnancies: highest risk during delivery
     - Rh (D) negative mother exposed to Rh (D) positive fetal RBCs
     - Rh(D) negative mother develops IgG antibodies against fetal RBCs
     - Maternal antibodies cross placenta, sensitize fetal RBCs, fetal RBCs destroyed by macrophages in fetal spleen
     - Severity of fetal anemia related to antibody concentration
   - Incompatibility
     - RH (D)
     - KELL
     - OTHER RH (C, c, E, e)
       • Managed similarly to Rh (D) alloimmunization
       • RhoGAM does not protect

2. Incidence, prevalence
   - Rh sensitization in 6.7/1000 live births in US in 2002
   - Worldwide incidence of clinically significant RBC antigen: 25/10,000 live births

3. Risk factors for any miscarriage
   - Race
     - Incidence of Rh(D) negativity highest in Caucasians (15%)
   - Parity
     - Incidence incr w/increasing parity

4. Morbidity / mortality
   - Fetal
     - Immune hydrops
     - Hydrops fetalis
     - Hyperbilirubinemia
     - Hemolytic anemia
   - Mortality in tertiary care centers, virtually zero

Diagnostics
1. History
   - Known prior history of maternal/paternal blood types
   - Previous sensitized pregnancy

2. Diagnostic testing
   - Antepartum
     - Maternal blood type and screen for serum antibodies
       - Indirect Coombs
         - Detects presence and titer of antibody
         - Most sensitive
     - Frequency of evaluation
       - First prenatal visit, 28 wks, delivery in uncomplicated Rh (D) negative mother
       - If alloimmunization is detected at a level of 1:8 or less, repeat antibody testing every 4 wks
       - If alloimmunization is detected at a level of 1:8 or greater, initiate fetal assessment (see therapeutics)
       - Alloimmunization to antigens other than D, use above titer level rules except for anti-Kell (Kell antibodies do not correlate w/fetal status)
     - Paternal Rh(D) testing
       - Caution parents about risk of false paternity
       - If heterozygous for Rh(D) or paternity is unknown proceed w/additional testing
       - If father of baby is Rh (D) negative, mom's antibodies will not harm Rh (D) negative fetus
     - Amniocentesis for fetal blood type (PCR)
       - Use if:
         - Maternal antibody screen is in critical range (>1:8) and paternal genotype is either unknown or positive (and heterozygous) for antibody in question
         - Paternal homozygous and positive for antibody then fetus is known to be at-risk and amniocentesis is not needed
       - Goal: to confirm an at-risk Rh(D) positive fetus
       - If negative, repeat maternal antibodies screen, 4-6 weeks
       - 1.5% false negative
   - Postpartum
     - Neonate
       - Direct Coombs
       - Blood type

Advanced Diagnostics
1. Accurate pregnancy dating
2. Repeat maternal Ab titers if initial Ab screen is positive
   - Every 4 weeks so long as titer is below critical level
     - Critical level for anti-D is between 1:8 and 1:32
   - If patient has had prior affected pregnancy OR titer levels are critical, fetal assessment is recommended
   - After initiating fetal assessments, maternal titers are no longer obtained
3. Non-invasive fetal assessment - Doppler assessment of Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV)
   o Indirect ultrasound assessment of fetal anemia
     ▪ If >1.5 MoMs (multiples of the median) fetal blood sampling needed
   o Safe but less accurate than direct measurement
   o Done every 1-2 weeks before 35 weeks gestation
   o After 35 weeks gestation false positive rate too high

4. Invasive fetal assessment - to identify and assess severity of anemia
   o Amniocentesis
     ▪ Indirect assessment of fetal anemia made from analysis of amniotic fluid bilirubin levels
       • If value suggests moderate to severe anemia, fetal blood sampling needed
       • Trend currently favors MCA Doppler instead
     ▪ Determine fetal blood type - if Rh(D) negative, no further maternal or fetal testing is needed
   o Fetal blood sampling PUBS (percutaneous umbilical blood sampling), cordocentesis, funipuncture)
     ▪ Directly measures hematocrit, direct Coombs, fetal blood type, reticulocyte count, total bilirubin
     ▪ Complications: 1-2% risk fetal loss

**Therapeutics**

1. Repeat ultrasound examinations
   o Not reliable to diagnose anemia until findings of hydrops are present, helpful only for other surveillance of fetus

2. Intrauterine fetal transfusion of RBCs if fetal hematocrit <30%
   o Can be done during diagnostic PUBS

3. Serial antenatal testing with nonstress tests or biophysical profiles

4. Delivery
   o Ideal age is controversial, refer to specialist
   o Induce at 37-39 weeks for mild anemia
   o Moderate to severe preterm anemia
     ▪ Weigh risks of antenatal interventions with risk of preterm delivery
     ▪ Neonatal survival at 32 weeks is greater than 95% in most neonatal intensive care nurseries
     ▪ Deliver after maternal steroid administration for enhanced fetal lung maturity
     ▪ Consider Phenobarbital
       • 30mg PO TID x1 week to accelerate hepatic maturity
       • Minimizes risk of neonatal exchange transfusion
       • Induce after one week of phenobarbital

**Follow-Up**

1. Depends on spectrum of disease
   o See therapeutics and diagnostics
2. Refer to maternal fetal specialist
   - Maternal titer >1:8
   - History of previous affected gestation

**Prognosis**
1. Effects of preterm delivery
2. Subsequent child development

**Prevention of Sensitization**
1. RhoGAM: for Rh negative mother who is not previously sensitized (unless biological father is known to be Rh negative)
   - Early pregnancy loss
     - 300ug dose of Rh (D) immunoglobulin if >13 weeks, give 50ug dose if <13 weeks
   - Elective abortion
     - 300ug dose of Rh (D) immunoglobulin if >13 weeks, give 50ug dose if <13 weeks
   - Amniocentesis
     - 300ug dose of Rh (D) immunoglobulin after procedure
   - After routine antibody testing at 24-28 weeks
     - 300ug dose of Rh (D) immunoglobulin
   - Postpartum
     - After delivery of an Rh positive or weakly Rh positive infant
     - Ideally within 72 hours of delivery
2. Maternal education
   - Clinical importance of:
     - True paternity
     - Reporting early miscarriages and bleeding to physician
     - Early and consistent prenatal care

**References**
Evidence-Based Inquiry

1. What is the best way to prevent isoimmunization in an Rh-negative patient with frequent first trimester spotting?

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