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)
    - Indirect ultrasound assessment of fetal anemia
        - If >1.5 MoMs (multiples of the median) fetal blood sampling needed
    - Safe but less accurate than direct measurement
    - Done every 1-2 weeks before 35 weeks gestation
    - After 35 weeks gestation false positive rate too high
4. Invasive fetal assessment -to identify and assess severity of anemia
    - 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
    - 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
    - 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%
    - Can be done during diagnostic PUBS
3. Serial antenatal testing with nonstress tests or biophysical profiles
4. Delivery
    - Ideal age is controversial, refer to specialist
    - Induce at 37-39 weeks for mild anemia
    - 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
    - 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

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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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