Rh Disease & Other Alloimmune Hemolytic Disorders in Pregnancy: A Fresh Look at an Old Problem

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Rh Disease:
(& Other Alloimmune Hemolytic Disorders in Pregnancy)
A Fresh Look at an Old Problem

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DISCLOSURES

• I have nothing to disclose.

OBJECTIVES

• Rh alloimmunization
  – Background
  – Pathophysiology
  – Management
  – Treatment
• Other common RBC antibodies

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BACKGROUND

• Red blood cells (RBC) have hundreds of antigens
• D antigen is part of the Rhesus blood group
  – Rh system: D, C, c, E, e, G
• “Rh(-)” is a misnomer
  – Rh(-) = D(-)

PATHOPHYSIOLOGY

• Rh(-) mother pregnant with Rh(+) fetus
• Maternal exposure to fetal RBCs
• Maternal B-cells recognize D antigen
• Short-lived IgM response
• Next pregnancy memory B-cells
  – Rapid development of anti-D IgG antibodies
  – IgG antibodies cross the placenta
  – Fetal hemolytic anemia

BACKGROUND

• Prevalence of Rh(-)
  – Basques 30-35%
  – Caucasians 15%
  – African 4-6%
  – Asian <1%
• Prevalence of Rh alloimmunization
  – 6.8/1000 live births in the U.S. 2003

PATHOPHYSIOLOGY

• Possible etiologies of alloimmunization
  – Fetomaternal hemorrhage
  – Blood transfusion error: D antigen variants
    • T&S Rh(-) but may weakly express D
    • Weak D also called D<sup>u</sup> antigen
    • Can cause anti-D antibody production in Rh(-) recipient
PATHOPHYSIOLOGY

Etiology of unexplained alloimmunization
- Unrecognized early miscarriages
  - Fetal RBCs express D antigen by day 38 (7w3d)
- Grandmother theory
  - Rh(+) mother pregnant with female Rh(-) fetus
  - Mother’s RBCs enter daughter’s circulation at birth
  - Rh(-) baby develops anti-D antibodies
  - Anti-D antibodies at 1st T&S in her 1st pregnancy

Variable amounts of exposure \( \rightarrow \) antibodies
- 1960s study of exposed Rh(-) male prisoners
  - As little as 0.1 mL \( \rightarrow \) antibodies
  - 2 exposures 10 mL + 5 mL \( \rightarrow \) 70% antibodies
  - As much a 450 mL \( \rightarrow \) only 80% antibodies
- Slow antibody response 5-15 weeks
  - 1st pregnancy usually not at risk of fetal anemia


Fetomaternal hemorrhage common
- Maternal presence of 0.01 mL fetal RBCs
  - 1st trimester 3%
  - 2nd trimester 12%
  - 3rd trimester 46%


Transplacental passage of maternal antibodies
- Anti-D IgG antibodies
- Antibodies opsonize fetal RBCs
  - Fetal RBC phagocytosis by splenic macrophages
- Hemolytic disease of the fetus or newborn
  - HDN or HDFN
- Fetal immune hydrops
  - Erythroblastosis fetalis
- IUFD or neonatal morbidity & mortality
MANAGEMENT

• Prevention
  – Identify Rh(-) women
    • T&S at 1st prenatal visit
    • Earlier T&S if bleeding and pregnant
    • Consider T&S at preconception counseling visits
  – Educate Rh(-) women about Rhogam
  – Father of the baby Rh testing
    • Rh positive → 60% heterozygous

MANAGEMENT

• Rhogam (anti-D immune globulin)
  – Pooled plasma with high anti-D antibody titer
    • Male volunteers purposely sensitized
  – 300mcg standard dose
    • Enough for 15mL fetal RBCs = 30mL whole blood
    • Covers 10% of average term newborn’s total blood volume
  – “Mini-rhogam” 50mcg
    • 2.5mL fetal RBCs
    • Lasts ~12 weeks
    • 15-20% still have low titer <1:4 at term
    • Anti-D antibody detection as long as ~26 weeks later

MANAGEMENT

• Rhogam routine dosing in the United States
  – 300mcg
    • 50mcg up through 12 weeks GA
  – Recheck antibody screen prior to administration
  – 28 weeks GA
  – Postpartum within 72hr of delivery
    • Up to 28 days later might still efficacious
• United Kingdom & Canada routine dosing
  – 100mcg
  – 28 + 34 weeks GA


MANAGEMENT

• Rhogam indicated if risk of fetomaternal hemorrhage
  – Pregnancy loss: SAB, TAB, ectopic pregnancy
  – Threatened abortion: vaginal bleeding
  – Invasive procedures
    • CVS, amniocentesis, MFPR, fetal surgery
  – Placental abruption
  – Bleeding previa
  – Trauma
    • MVA, ECV
  – IUFD
MANAGEMENT

- Rhogam mechanism of action
  - Anti-D prophylaxis: passive anti-D IgG
  - Epitope masking
    - Fetal RBC D antigens covered by passive anti-D IgG
    - Fetal RBCs cleared/destroyed without alloimmunization
    - INCOMPLETE epitope masking
  - Down-regulation of antigen-specific B cells

- Before the standard use of rhogam:
  - High alloimmunization rates
    - 2 non-compatible pregnancies → 16%
  - After standard use of postpartum rhogam:
    - Lowered alloimmunization rate → 2%
  - And 3rd trimester + Postpartum rhogam:
    - Even lower alloimmunization rate → 0.1%

- Testing for fetomaternal hemorrhage
  - Rosette test
    - Qualitative → +/- result
  - Kleihauer-Betke
    - Quantitative
    - Volume of hemorrhage
    - % fetal blood cells x 50

MANAGEMENT

- Four rhesus immune globulin brands
  - RhoGAM® (Ortho-Clinical Diagnostics, NY)
    - IM due to IgA contaminants
  - HyperRHO® (Talecris, NC)
    - IM due to IgA contaminants
  - Rhophlac® (ABO Pharmaceuticals, CA)
    - IV or IM (IgG only)
  - Win-Rho-SDF® (Cangene Corporation, Canada)
    - IV or IM (IgG only)
    - Thimerosal free
MANAGEMENT - OLD

- Maternal anti-D antibodies → Fetal Rh status
  - Father of the baby (FOB) Rh status
    - Genotype if Rh(+)
      - 60% chance heterozygote
      - If heterozygote, 50% chance fetus will be Rh(-)
  - Amniocentesis if FOB heterozygous or unknown
  - Serial anti-D titers q4 wks if fetus Rh(+) or ?
    - Increase titers to q2 weeks after 24 wks GA
  - Laboratory critical titer >1:8 – 1:32

MANAGEMENT - NEW

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  - Father of the baby (FOB) Rh status
    - Genotype if Rh(+)
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  - Amniocentesis if FOB heterozygous or unknown
  - Maternal serum cell free fetal DNA
    - Rh D gene on short arm chromosome 1
    - Apoptosis of placental trophoblasts
      → fetal DNA in maternal system
    - Europe using cffDNA routinely for fetal Rh
  - Avoid unnecessary rhogam in ~40% of Rh(-)♀
    - 99.3 – 100% sensitivity

AUDIENCE RESPONSE QUESTION

Maternal serum cell free fetal DNA (NIPT) is useful in the management of Rh alloimmunization because:

A. You should rule out aneuploidy before considering treatment of fetal anemia
B. Fetal gender affects prognosis
C. NIPT can detect fetal Rh status

MANAGEMENT - NEW

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  - Rh D gene on short arm chromosome 1
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    → fetal DNA in maternal system
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Clausen et al. Transfusion 2012;52(4):752
Wikman et al. Obstet Gynecol 2012;120(2Pt1):227
MANAGEMENT - OLD

• Rise in titers or previously affected pregnancy
  – Referral to MFM for co-management
• Antenatal testing starting at 32 weeks GA
• Amniocentesis for ΔOD450
  – Bilirubin levels in the amniotic fluid
  – Liley curve → Queenan curve
  – Predict severity of fetal anemia


AUDIENCE RESPONSE QUESTION

Moderate to severe fetal anemia can be detected using ultrasound doppler of the:

A. Umbilical artery
B. Umbilical vein
C. Ductus venosus
D. Middle cerebral artery

MANAGEMENT - NEW

• Rise in titers or previously affected pregnancy
  – Referral to MFM for co-management
• Antenatal testing if viable gestational age
• Amniocentesis for ΔOD450
  – Liley curves to predict severity of fetal anemia
• Middle cerebral artery peak systolic velocity (MCA PSV)

MANAGEMENT - NEW

• MCA PSV
  – Non-invasive screening for severe fetal anemia
  – Weekly ultrasound with doppler > 18 wks GA
  – Avoids ~50% of unnecessary PUBS
  – Detection of moderate - severe fetal anemia
    • MCA PSV ≥ 1.5 MoM
    • Sensitivity 100%
    • False positive rate 12%
    • Not validated for >35 weeks gestation

Mari et al. NEJM 2000;342:9-14
TREATMENT

• Percutaneous umbilical blood sampling (PUBS)
  – Cordocentesis or funipuncture
  – Confirm severe anemia
  – Calculate ideal transfusion amount
  – 1-2% procedure-related rate of fetal death
• Intrauterine transfusion (IUT)

TREATMENT

• Intraperitoneal transfusion
  – Sir William Liley 1963
• IUT possible with improved ultrasound
  – Perinatal survival rates ~90%
    • Lower if hydrops, ~78%
  – Long-term normal neurologic outcomes >90%
  – High-risk for needing serial transfusions until 3 months of life due to persistent maternal antibodies

TREATMENT

• Late preterm/early term delivery
  – MCA PSV stays <1.5 MoM → 38 week delivery
  – Fetal anemia + >35 wks GA → delivery
• Antepartum phenobarbital in certain cases
  – Maturation of the fetal liver for bilirubin clearance

TREATMENT

• Investigational therapy for women with RH disease & prior severe early fetal anemia
  – Maternal plasmapheresis
    • Single volume plasmapheresis QOD x 3 at 12wks GA
  – IVIG following final plasmapheresis
    • 1g/kg slow infusions 2 days in a row
    • 1g/kg slow infusion every week until 20wks GA

TREATMENT

• Preconception counseling
• Prevent subsequent pregnancy with HDFN
  – Future conception with Rh(-) donor sperm
  – IVF with preimplantation genetic diagnosis
    • Father of the baby Rh D heterozygote
    – Gestational surrogate

• Future prevention of severe fetal anemia
  – Immunization to paternal leukocytes
    • Rabbit model
  – Ameliorate anti-D response in subsequent pregnancy
    • Intranasal spray RhD peptides
    • Transgenic mouse model


AUDIENCE RESPONSE QUESTION

The number of other non-D RBC antigens that can cause HDFN is:

A. 1  B. 2-5  C. 6-10  D. >10

OTHER BLOOD GROUP SYSTEMS

• Non-D Rh
  – E, C, c  Mild to severe HDFN
  – Lewis & I
    – Le^a and Le^b  No risk (IgM), routine care
    – I  No risk (IgM), routine care

• Kell
  – K  Mild to severe HDFN
    – k, Ko, Kp^{a+b}, J_s^{a+b}  Low risk, routine care
    – Transfused blood not cross-matched for Kell

OTHER BLOOD GROUP SYSTEMS

• Duffy
  – Fy\textsuperscript{a}  Mild to severe
  – Fy\textsuperscript{b}, By\textsuperscript{3}  Low risk

• Kidd
  – Jk\textsuperscript{a}  Mild to severe
  – Jk\textsuperscript{b}, Jk\textsuperscript{3}  Low risk

• MNSs
  – M, S, s, U, Mi\textsuperscript{a}  Mild to severe
  – N  Low risk

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