Management of Red Cell Alloimmunization

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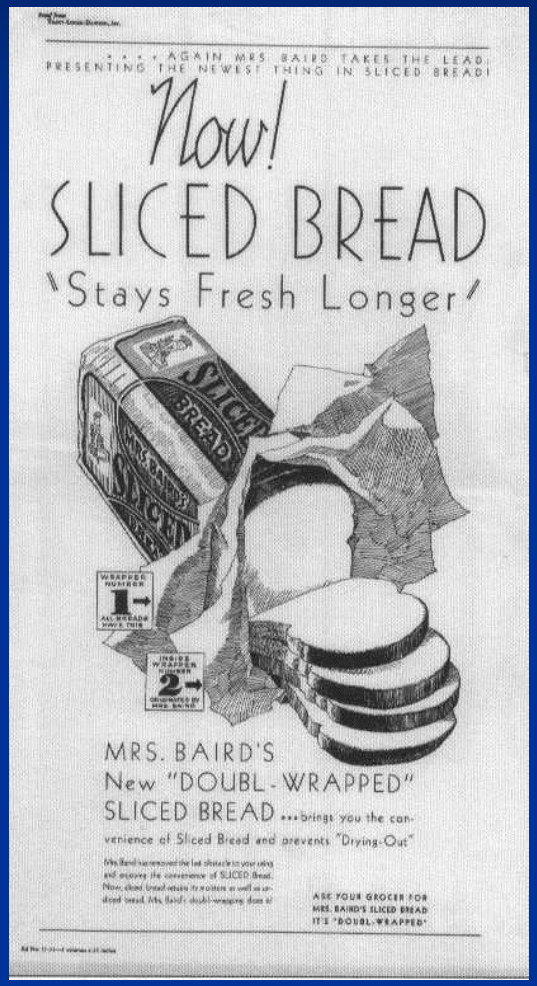
Goals

- Discuss red cell alloimmunization
  - Pathogenesis
  - Diagnosis
  - Prevention strategies
  - Management

Where to Find Answers

- ACOG Practice Bulletin
  - Management of Alloimmunization During Pregnancy (#75, August 2006)
  - Prevention of Rh D Alloimmunization (#4, May 1999)
- Up-to-Date
- Project ECHO

We have come a long way…



- Rh D Alloimmunization:
  - Previously, 10-16% of at-risk pregnancies became immunized
  - Rates reduced 90% by post-partum Rh D immune globulin
  - Rh D immune globulin at 28 weeks reduces incidence from 2 to 0.1%

But, we have a ways to go…

- Continued Rh D alloimmunization
  - Failure to administer at 28 weeks
  - Failure to recognize events that place patients at risk
  - Failure to administer postnatally
  - Spontaneous immunization despite treatment (0.1-0.2%)
- Continued non-Rh D alloimmunization
  - No available preventative therapy

What is Alloimmunization?

- Immunization of an individual by the introduction of antigens from *another individual of the same species*
  - Red cell antigens
  - Maternal red cell alloimmunization develops as a result of maternal immune system exposure to incompatible fetal RBCs

How Does Alloimmunization Cause Anemia?

- Antibodies (IgG) cross the placenta and bind to fetal RBCs for destruction by macrophages in the fetal spleen
- Component of bone marrow suppression in Kell alloimmunization

What Types of Red Cell Alloimmunization Are There?

- Nomenclature of the blood group systems
  - Rh (DEC)
    - D or null (Rh "negative" or "positive")
      - There is no "d"
      - Positive: 60% are homozygous, 40% are hetero
      - Negative
        - 15% of Caucasians are D negative
        - 8% of African Americans
    - E or e
    - C or c

What Types of Red Cell Alloimmunization Are There?

- Nomenclature of the blood group systems
  - Non-Rh antibodies
    - Kell antigen system
    - MNS system
    - Duffy
    - Kidd
    - The list goes on…

How Do These Antigen Types Correspond to Risk for HDFN?

- Frequently associated with severe disease
  - Rh D
  - Rh c
  - Kell (K1)
- Infrequently associated with severe disease
  - Other Rhesus antigens
  - Duffy (Fy^a)
  - Kell (K2)
  - Kidd (Jk^a)
  - MNS antigens
- Associated with mild disease
  - Duffy (Fy^b)
  - Kidd (Jk^b)

How Do You Diagnose Alloimmunization?

- Antibody screen
  - 1st prenatal visit
  - +/- 28 weeks
  - On admit to labor and delivery
- Positive screen- Next steps?
  - Check the antibody type and titer
    - Higher titer = more antibodies (1:2 vs 1:64)
  - Look up the association with HDFN
  - Obtain a good history

What Do You Ask the Patient?

- What do you want to establish?
  - Mechanism of alloimmunization
    - Fetomaternal hemorrhage
    - Transfusion
  - Timeframe of sensitization
  - Whether this is the first affected pregnancy
  - Whether this fetus is at risk

What Do You Ask the Patient?

- Detailed obstetrical history
  - Don't forget miscarriages, terminations, ectopics, stillbirths…
  - When was the first positive antibody screen?
  - Did she have prenatal labs drawn with all her pregnancies?
  - Did she receive Rhogam when indicated? (if Rh negative)
- Neonatal history
  - Prematurity?
  - Blood transfusions?
  - Hyperbilirubinemia (Bili Lights)?
- Same father of the baby?
  - Is paternity certain?
  - Is paternal blood type known?

Management of Alloimmunization

- Similar for Rh D and other antibodies
- Step 1: Determine if the fetus is affected
- Paternity certain
  - Paternal phenotype
    - Phenotype negative = no risk
  - If positive phenotype, consider genotype
    - If homozygous positive = fetus at risk
    - If heterozygous = 50% risk of affected fetus

Detection of Fetal Antigen status

- Phenotype
  - Fetal blood sampling
- Genotype
  - Fetal blood
  - Amniocentesis
  - CVS
  - Cell free DNA (D)

Management of Alloimmunization

- First affected pregnancy vs. subsequent
  - Fetal effects tend to be mild in first affected
  - Tends to worsen with each pregnancy
- First affected
  - Follow titers
    - Screening test
    - Positive titer means "fetus is at risk" not "affected"
    - Use the same lab (variability)

Management of Alloimmunization

- First affected
  - Concept of CRITICAL TITER
    - Titer = integer of the greatest tube dilution with a positive agglutination reaction
    - 1:16 for most labs
    - Indicates risk of severe anemia
    - Assess titers every 4 weeks from 18-24 weeks until delivery
    - Once critical titer is reached, further evaluation is necessary
      - MFM re-referral is indicated at this point

Management of Alloimmunization

- Previous affected
  - Fetal hydrops, intra-uterine transfusion, preterm delivery for fetal anemia, neonatal transfusion
  - Titers not reliably predictive of severity of anemia in this situation
  - Start assessment of fetal anemia at 18-20 weeks gestation
  - MFM referral indicated in the 1st trimester

Management of Alloimmunization

- MFM referral or case review in the first trimester in all cases can be helpful
  - May be able to determine that the fetus is unaffected
  - May lead to case-specific alterations in management

Case

- 25 year-old G4P2012
- Anti-E antibodies
- Titer 1:2
- MANAGEMENT?
  - First affected pregnancy
  - Second affected pregnancy

Key Questions

- Is the antibody associated with HDFN?
- What is the titer?
- Is the fetus at risk?
  - Detailed history
  - Paternal antigen status
  - Diagnostic tests