Prevention of Rh D Alloimmunization

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Nomenclature

- The RBC membrane contains many anchored surface proteins.
- A blood group system consists of one or more antigens controlled at a single locus, or by two or more closely linked homologous genes with no recombination.
- 30 human blood group system genes have been identified and sequenced.
- Many terminologies have been used to denote human blood groups.
- Most common groups: ABO and Rh
Different types of Rh types include: D, C, c, E, and e.

Women who carry Rh D Antigen are considered Rh (D) positive.

Frequency of Rh D negative phenotype is:
- European and North American descent (~15%)
- African and India (3-8%)
- Asia (0.1-0.3%)
Nomenclature

- **Alloimmunization** - immunologic reaction against foreign antigens that are distinct from antigens on an individual’s cells.

- The most commonly discussed type of alloimmunization refers to **Rh D alloimmunization**.
  - This refers to the maternal formation of antibodies against fetal Rh D.

- **Rhogam** - Rh D immunoglobulin or anti-D immune globulin - immune globulin used specifically to bind to Rh D antigen
Causes of Rh D Allo-immunization

- Occurs when a Rh D negative woman is exposed to RBCs expressing Rh D antigen
- This can occur when there is antenatal mixing of maternal and fetal blood, even in asymptomatic individuals.
First pregnancy with Rh\(^+\) fetus

1. Rh\(^-\) mother
2. Anti-Rh antibodies are produced upon exposure to fetal Rh antigens.
3. Anti-Rh antibodies bind and inactivate fetal Rh antigens before they stimulate immune response in mother.
4. Maternal anti-Rh antibodies attack and destroy fetal Rh\(^+\) red blood cells. Fetus becomes hemolytic.

Second pregnancy with Rh\(^+\) fetus

1. Rh\(^-\) mother
2. Rh\(^+\) red blood cells enter into mother’s circulation.
3. Anti-Rh antibodies remain in mother’s circulation and cross placenta.
4. Maternal anti-Rh antibodies attack and destroy fetal Rh\(^+\) red blood cells. Fetus becomes hemolytic.

First pregnancy with Rh\(^+\) fetus and anti-Rh antibody treatment

1. Rh\(^-\) mother
2. Rh\(^+\) red blood cells enter into mother’s circulation.
3. Anti-Rh antibodies bind and inactivate fetal Rh antigens before they stimulate immune response in mother.
4. Mother injected with Rho(D) immune globulin during pregnancy.
Box 1. Potential Sensitizing Events in Rh D-Negative Women in Pregnancy

- Chorionic villus sampling, amniocentesis, cordocentesis
- Threatened miscarriage or miscarriage
- Ectopic pregnancy
- Evacuation of molar pregnancy
- Therapeutic termination of pregnancy
- Antepartum hemorrhage
- Abdominal trauma
- Intrauterine fetal death
- External cephalic version
- Delivery
Rates of feto-maternal hemorrhage:

- 3-11% of women with threatened abortion (miscarriage) in first trimester
- 45% after third trimester delivery
- 1-2% after spontaneous abortion
- 4-5% after uterine instrumentation
- 14% after chorionic villus sampling
- 2-6% for amniocentesis or cordocentesis
• Rhogam, or Anti-D immune globulin is extracted by cold alcohol fractionation from donated plasma.

• One prophylactic dose (300 mcg) of Rhogam can prevent Rh D alloimmunization after exposure to up to 30 mL of Rh D positive fetal whole blood.
Anti-D Immune Globulin to Prevent Allo-immunization

- All Rh D negative women at 28 weeks gestation should receive prophylactic Rhogam
- Rhogam should be given sooner if concern for feto-maternal hemorrhage
- After delivery, all neonates’ blood type is tested.
  - If an Rh D negative woman gives birth to Rh D negative neonate, no Rhogam indicated.
  - If an Rh D negative woman gives birth to Rh D positive neonate, Rhogam work-up needs to be done and Rhogam needs to be given.
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- Rhogam should be given within 72 hours of delivery.
Screening for feto-maternal hemorrhage

Assessing need and dosing (if large maternal-fetal hemorrhage is suspected), can be done using the Kleihauer-Betke and Rosette Test.

**Rosette Test:**
- Qualitative test
- Can detect minimum of 10 mL fetal blood in maternal circulation
- If negative, standard dose Rhogam sufficient
- If positive, use KB test

**Kleihauer-Betke Test:**
- Quantitative test
- Determines amt of fetal blood
- Fetal whole blood (mL) = % fetal cells x 5000 mL of maternal blood
Failure to Prevent Rh D Alloimmunization

- Alloimmunization of Rh D negative woman may still occur.
- May be due to the following:
  - Failure to administer Rhogam altogether
  - Insufficient dosage
  - Untimely administration of Rhogam (>72 hours)
  - Unrecognized maternal-fetal hemorrhage during pregnancy
- Approximately 0.1-0.4% of women at risk become sensitized during pregnancy.
- Spontaneous immunization despite adherence can occur 0.1-0.2%. Thus prophylaxis is not 100% effective.
Is Rhogam indicated in sensitized pregnancy? -NO!

- All pregnant women should be tested for ABO blood group and Rh D type and presence of antibodies.
- If anti-D antibody is identified, further history should be obtained.
  - I.e. Did patient patient previously receive Rhogam, presence of another pregnancy that patient did not disclose.
- If patient is found to have anti D antibodies due to sensitization, Rhogam is not beneficial and should proceed in accordance with protocols in treating alloimmunization.
How should one deal with issue of paternity?

- If paternity is **certain** and the father is known to be Rh D negative, antenatal prophylaxis is not necessary.
  - BEWARE: MEAN NON-PATERNITY POPULATION RATE = 3%
- If the Rh type of the partner is not known, routine antenatal Rhogam prophylaxis is preferred.
How should weak D blood type be managed?

• An estimated 0.2 - 1% of Caucasian individuals inherit genes that code for serologic weak D phenotypes.

• Some individuals express reduced numbers of normal Rh D antigens whereas others express partial or abnormal Rh D antigens.

• Therefore, it is possible to develop antibodies against part of Rh D antigen that they are missing and if exposed to Rh D positive blood.

• Thus, Rhogam indicated in patients with weak Rh D blood type.
How long does the effect of Rhogam last?

- Median half-life is 23 days
- If delivery occurs within 3 weeks of previous Rhogam administration, post-natal dose may be withheld (if low suspicion for excessive maternal fetal hemorrhage)
  - Can assess with KB test
Should Rhogam be withheld from woman undergoing postpartum sterilization?

• NO! Rhogam should NOT be withheld for woman that are planning to undergo postpartum sterilization.
• Pregnancies occur despite sterilization (either naturally or via ART)
• Alloimmunization complicates crossmatching of blood products in the future.
What should be done if pt discharged home prior to Rhogam administration?

- Ideal time to administer Rhogam is 72 hours
- Some benefit seen for patients as late as 28 days
Questions?