ALLOIMMUNIZATION IN PREGNANCY
Erythroblastosis Fetalis (Red Cell Alloimmunization)

- The first description of erythroblastosis fetalis (hemolytic disease of the newborn) dates back to 1609.
- Until the early 1900s, the role of alloimmunization in the pathogenesis of erythroblastosis was established.
- In the past, Rh alloimmunization also has been referred to as Rh sensitization or Rh isoimmunization.
ERYTHROBLASTOSIS FETALIS

Rh-negative woman and Rh-positive man conceive a child
Rh-negative woman with Rh-positive fetus
Cells from Rh-positive fetus enter mother's bloodstream
Woman becomes sensitized—antibodies (⁺) form to fight Rh-positive blood cells
In the next Rh-positive pregnancy, maternal antibodies attack fetal blood cells
Genetics of the Rh Antigen

- three genetic loci, each with two major alleles, lettered C, c, D, E, and e.
- The Rh gene complex is described by the three appropriate letters with eight possible combinations (listed in decreasing order of frequency among whites): CDe, cde, cDE, cDe, Cde, cdE, CDE, and CdE.
- Rh positive indicates the presence of the D antigen
- Rh negative indicates the absence of D antigen on erythrocytes.
Pathophysiology of Rh Alloimmunization

Rh D alloimmunization can occur only in the presence of three conditions:

(a) the fetus must have Rh-positive erythrocytes, and the mother must have Rh-negative erythrocytes;

(b) the mother must have the immunogenic capacity to produce antibody directed against the D antigen;

(c) a sufficient number of fetal erythrocytes must gain access to the maternal circulation.
Incidence of Rh D Incompatibility and Subsequent Alloimmunization

- About 10% of pregnancies are Rh incompatible
  - fewer than 20% of Rh-incompatible pregnancies result in alloimmunization

- About 16% of untreated Rh-negative women become alloimmunized in their first Rh-incompatible (ABO-compatible) pregnancy
  - Half produce detectable anti-D antibody within 6 months of delivery,
  - rest have undetectable amounts until early in the next incompatible pregnancy

- before the introduction of Rh immune globulin prophylaxis, only about 1% of pregnant women had anti-D antibody
Maternal Immunologic Response:

- 30% of Rh-negative individuals appear to be immunologic “nonresponders” who will not become sensitized.

- ABO incompatibility diminishes the risk of alloimmunization to about 1.5% to 2.0% after the delivery of an Rh-positive fetus.
  - The effect is most pronounced if the mother is type O and the father is type A, B, or AB.
Fetomaternal Hemorrhage

- Fetal red cells may gain access to the maternal circulation:
  - during pregnancy,
  - During delivery:
  - the immediate postpartum period
Fetomaternal Hemorrhage

- **During delivery:**
  - 15-50% of births
  - The amount of fetal blood entering the maternal circulation is usually less than 0.1 mL but may be greater than 30 mL in 0.2% to 1.0% of cases.
Fetomental Hemorrhage

- immediate postpartum period:
  - Risk factors:
    - cesarean delivery
    - multiple gestations,
    - bleeding placenta previa or abruption,
    - manual removal of the placenta,
    - intrauterine manipulation.

- However, the majority of cases of excessive fetomaternal hemorrhage occur after uncomplicated vaginal delivery.
Rh D Immune Globulin and the Prevention of Rh D Alloimmunization

- antibody-mediated immune suppression
- the amount of Rh D immune globulin necessary to prevent alloimmunization varies according to the size of fetomaternal hemorrhage:
  - 300 µg of Rh D immune globulin for exposure to 10 mL of fetal blood
  - 20 µg of Rh D immune globulin for exposure to 1 mL of fetal erythrocytes
  - 10 µg of Rh D immune globulin for 1 mL of whole fetal blood
Postpartum Alloimmunization Prophylaxis

- administration of Rh D immune globulin
  - a dose of 100 Âµg to 150 Âµg
  - within 72 hours of delivery
Postpartum Alloimmunization Prophylaxis

- Rh D immune globulin should be given as soon as possible after exposure to Rh D-positive blood (delivery or other event associated with fetomaternal hemorrhage) and before the primary immune response is established.
- If for some reason Rh D immune globulin prophylaxis does not occur within 72 hours after exposure, susceptible Rh D-negative women should be treated up to 14 to 28 days.
- If the neonatal Rh status is unknown 3 days after delivery, Rh D immune globulin should be given rather than waiting for the neonatal results.
Antepartum Alloimmunization Prophylaxis

- Prophylactic administration of Rh D immune globulin at 28 weeks gestation reduces the incidence of alloimmunization from 1.8% to 0.1%
Management of the Unsensitized Rh-Negative Pregnant Woman

- Every woman should have her ABO blood group, Rh type, and antibody screen checked at the first prenatal visit of all pregnancies.

- If she is Rh-negative or weak D-negative and has no demonstrable antibody,
  - she is a candidate for 300 μg Rh D immune globulin prophylaxis at around 28 weeks gestation and again immediately postpartum.
Management of the Unsensitized Rh-Negative Pregnant Woman

- obtaining another antibody screen before administration of Rh D immune globulin, in
- After delivery, another antibody screen is routinely performed. If negative and the newborn is Rh D positive or weak D positive, women should be given 300 Âµg of Rh D immune globulin including antepartum prophylaxis
Management of the Unsensitized Rh-Negative Pregnant Woman

- because a small number of deliveries (0.1% to 1.0%) result in a fetomaternal hemorrhage greater than 30 mL:
  - a screen for “excessive” fetomaternal hemorrhage should be performed routinely
    » use the erythrocyte rosette test
    - If positive: the volume of fetal red cells in the maternal circulation can be calculated by using the Kleihauer-Betke test, if >30 ml:
      - an additional 10 Âµg of Rh D immune globulin should be administered for each additional milliliter of fetal blood.
Management of the Unsensitized Rh-Negative Pregnant Woman

Figure 18.4 Diagram outlining the management of Rh D-negative, nonalloimmunized pregnancy.
Management of the Unsensitized Rh-Negative Pregnant Woman

- A weak D-"positive mother who delivers an Rh-positive infant is not at significant risk of Rh alloimmunization

- Occasionally, a woman previously typed as Rh negative is unexpectedly found to be weak D positive during pregnancy or after delivery
  - if fetomaternal hemorrhage is found:
    » the mother should be treated with Rh D immune globulin.
Management of the Unsensitized Rh-Negative Pregnant Woman

First-trimester complications result in fetomaternal hemorrhage sufficient to alloimmunization:
- spontaneous miscarriage,
- elective abortion
- ectopic abortion

Women with threatened first-trimester miscarriage
- only occasionally is associated with alloimmunization
Management of the Unsensitized Rh-Negative Pregnant Woman

- patient who has antepartum bleeding or suffers an unexplained second- or third-trimester fetal death:
  - should receive Rh D immune globulin prophylaxis
  - be evaluated for the possibility of massive fetomaternal hemorrhage.
Management of the Unsensitized Rh-Negative Pregnant Woman

- Several procedures also may result in fetomaternal hemorrhage sufficient to cause alloimmunization:
  - chorionic villus sampling (CVS)
  - amniocentesis
  - external cephalic version.
Management of the Unsensitized Rh-Negative Pregnant Woman

- For first-trimester pregnancy complications and procedures:
  - 50 Âµg of Rh D immune globulin is protective.
  - Beyond 12 weeks, a full 300-Âµg dose is indicated, even in the absence of detectable hemorrhage.
  - In second & third trimester: an assessment of the volume of fetal whole blood should be performed, and the appropriate amount of Rh D immune globulin should be given.
Management of the Unsensitized Rh-Negative Pregnant Woman

- Failure to administer Rh D immune globulin when indicated may due to:
  - Failure to type the patient's blood at the first prenatal visit or to order Rh D immune globulin when indicated
  - Error in transmitting the proper blood type to the mother's chart and to the physician
Management of the Unsensitized Rh-Negative Pregnant Woman

- ...  
- Error in typing the mother, father, or baby's blood  
- Failure to administer Rh D immune globulin when ordered  
- Unrecognized fetomaternal hemorrhage during pregnancy  
- Inadequate Rh D immune globulin for the volume of fetomaternal hemorrhage  
- Patient refusal
Management of the Rh D- Alloimmunized Pregnancy

- **mildly affected fetuses:**
  - can be allowed to remain in utero until they have achieved pulmonary maturation

- **moderately to severely affected fetuses:**
  - may need intrauterine treatment (transfusion) and very likely will require delivery prior to pulmonary maturation.