Overview of Hemolytic Disease of the Fetus and Newborn (HDFN)

INTRODUCTION

Hemolytic disease of the fetus and newborn (HDFN) is an alloimmune condition in which the lifespan of the cells in the fetus or newborn is shortened by the specific maternal antibodies that have passed through the placenta. The red blood cells are broken down and reticulocytosis and anemia may develop. The resulting condition may be moderate or severe.

HDFN is also called erythroblastosis fetalis because erythroblasts are present in the fetus or newborn’s blood.
- “hemolytic” means breaking down of red blood cells
- “erythroblastosis” refers to making of immature red blood cells
- “fetalis” refers to the fetus

Alloimmunization

HDFN may be caused by maternal exposure to a foreign antigen and production of IgG antibodies. The IgG antibody will target the antigen, if present in the fetus, and may affect the fetus in utero and persist after delivery.

- Maternal sensitization may occur due to trauma, abortion, childbirth, ruptures in the placenta during pregnancy, or medical procedures carried out during pregnancy, that breaches the uterine wall.
- Another cause of maternal alloimmunization may be a blood transfusion with an incompatible blood type. Rarely is D-positive red blood cells transfused to a D-negative female of childbearing age. The D antigen is the most potent immunogen; 30%-85% of D-negative persons who receive D-positive red cell transfusion would develop anti-D. HDFN caused by anti-D is the classic example of maternal alloimmunization in which the D-negative mother carries a D-positive fetus. In addition to anti-D, anti-K and anti-c are the common causes of HDFN. HDFN caused by anti-K is unique in that anti-K produces suppression of fetal erythropoiesis in addition to hemolysis.
- A third type of sensitization can occur in group O women. While anti-A and anti-B found in groups B and A, respectively, are primarily IgM, anti-A,B in group O is primarily IgG, which can cross the placenta. IgG anti-A,B (and any IgG anti-A and IgG anti-B) can cause HDFN, but it is usually mild. When ABO incompatibility between mother and fetus is present (e.g, group O mother and group A fetus), it has a protective affect in that D alloimmunization is less likely to occur.
DIAGNOSIS AND MANAGEMENT

A diagnosis of HDFN can be made based on the following information, tests or procedures:

Prenatal

- Patient history provided by the mother is the first step in diagnosing HDFN. A previous history of alloimmunization, miscarriage, or a "sick" baby should alert the attending physician to possible concerns. Prenatal screening includes ABO/Rh typing and an antibody screen. ABO/Rh and antibody screen are performed as early in pregnancy as possible, preferably during the first trimester. If the antibody screen is reactive, the antibody specificity must be determined. Further testing will depend on the antibody specificity and its immunoglobulin class, IgM or IgG. IgM antibodies can be ignored.
- Depending on the results of the antibody screen, maternal antibody titer is performed and paternal antigen status is determined by molecular testing. If the father is heterozygous for RHD, the fetus has a 50% chance of being either Rh-positive or negative. If the father is homozygous for RHD, the fetus will be Rh-positive and will be at risk of HDFN. The fetus’ DNA genotype can be determined using maternal plasma or amniotic fluid as early as 18 weeks of gestation.
- An antibody titration is a measure of the strength of an antibody by testing its reactivity at increasing dilutions against the appropriate antigen. Antibody titrations can help in decisions about the timing of intervention.
- Doppler ultrasonography is a noninvasive procedure used routinely to determine the clinical status of the fetus. Fetal anemia causes an increase in cardiac output so the peak systolic velocity of the middle cerebral artery (MCA) is measured.
- Ultrasonography can provide information on polyhydramnios (excesses of amniotic fluid), fetal organomegaly (organ enlargement) and edema (body fluid buildup particularly in the fetus’ abdomen). Serial sonograms are used to monitor fetal development.
- Cordocentesis or Percutaneous Umbilical Sampling (PUBS) uses high-resolution ultrasound with color Doppler enhancement of blood flow to visualize the umbilical vein at the level of the cord insertion into the placenta. A needle is inserted into the umbilical vessel and the fetal blood specimen obtained can be used for testing including fetal blood type, bilirubin, and hemoglobin.
- Amniocentesis is a test performed to determine chromosomal and genetic disorders and certain birth defects. The test involves inserting a needle through the abdominal and uterine walls into the amniotic sac to retrieve a sample of amniotic fluid. Bile pigments in the amniotic fluid can also be measured.
- Amniocentesis and cordocentesis have risks including infection, premature labor, and trauma to the placenta, which may cause increase fetomaternal hemorrhage. Cordocentesis is associated with a 1% to 2% risk of fetal morbidity and mortality.

Neonatal

- Cord blood testing is performed to determine the ABO, Rh, direct antiglobulin test, and occasionally, bilirubin levels. Maternal blood test results must also be considered in the evaluation.
- Heelstick specimens are used to determine hemoglobin and bilirubin levels.
Positive DAT in Infant
1. Check the mother's ABO and antibody screen results.
2. Mother is group O with a negative antibody screen, and infant is not group O: the positive DAT is likely the result of ABO isoimmunization – the mother's IgG anti-A,B (and any IgG anti-A/anti-B) may have coated the infant's A or B cells.
3. If the mother's antibody screen is negative, the antibody coating the infant's cells may be directed against a low-prevalence antigen. The infant probably inherited an antigen from the father to which the mother has made the antibody. Test the mother's plasma with cells carrying low-prevalence antigens or test the baby's eluate with the father's red cells.
4. Eluate testing is not necessary in these situations:
   a. Clinically insignificant antibody in the mother
   b. Anti-D identified in the mother is due to RhIG administration
   c. The mother is group O with negative antibody screen, and the infant is non-O, the infant's cells are likely sensitized with anti-A,B. ABO isoimmunization is the most likely cause of the positive DAT.

TREATMENT

Once HDFN is diagnosed, treatment will be determined based on several factors:

- The gestational age, overall health, and medical history of the fetus.
- The fetus' tolerance for specific medications, procedures, or therapies.
- The parent's opinion, preference, and expectations.

During pregnancy, treatment for HDFN may include:

- Intrauterine blood transfusion (IUT) of red blood cells into the baby's circulation is best accomplished using the direct intravascular approach by the umbilical vein (PUBS). The fetus may need to be sedated to keep the baby from moving. Blood for IUT is crossmatched with the mother's serum and is compatible with both the infant and mother. IUTs may need to be repeated as often as every two weeks.
- The blood selected for an IUT should meet the criteria listed below. If the mother has an antibody to a high-prevalence antigen, she may donate her blood for the IUT.
  - Group O, Rh negative, or negative for the antigen corresponding to the mother's antibody if the specificity is not anti-D.
  - Irradiated to prevent the possibility of graft-versus-host (GVH) disease.
  - Cytomegalovirus-reduced-risk (CMV-) as this virus can attack the fetus.
  - Hemoglobin S negative to maximize oxygen-transporting capacity in the setting of low oxygen tension.
  - Fresh (e.g., less than 7 days) for optimal survival of transfused cells.
  - Hematocrit typically 75-85% or as requested by the physician.
  - If the mother's red cells are used, they should be washed prior to transfusion to remove the offending antibody(ies).
- Early delivery of the fetus may be necessary if complications arise. If the lungs are not developed, early delivery poses a greater risk.

After delivery, several treatment options exist:

- Blood transfusions are administered for severe anemia.
- Intravenous fluids are infused for low blood pressure. Sodium bicarbonate may be used for correction of acidosis.
- Respiratory distress is helped by providing oxygen or a mechanical breathing machine.
- Exchange transfusions are given to replace the baby's damaged blood with fresh blood. The exchange transfusion helps remove circulating maternal antibodies and antibody
coated neonatal red blood cells, increase the hemoglobin, and lower bilirubin levels. The neonate’s blood is exchanged by alternating withdrawing and transfusing small amounts of blood through a vein or artery. Exchange transfusion may need to be repeated if the bilirubin levels remain high. Blood for exchange transfusion is crossmatched with the mother’s serum and is compatible with both the infant and mother. Blood used for an exchange transfusion is either fresh WB (rare) or packed red blood cells reconstituted with fresh plasma.

- Phototherapy is used to treat mild HDFN.

### COMPLICATIONS OF HDFN

- Kernicterus—a condition with severe neurological symptoms, associated with high levels of bilirubin in the blood.
- Hepatosplenomegaly—enlargement of the liver and spleen.
- Inspissated (thickened or dried) bile syndrome—biliary obstruction caused by plugging of the outflow tract.
- Hemolytic anemia—reduction below normal in the quantity of hemoglobin caused by the destruction of red blood cells.
- Liver damage—damage to the liver due to excess bilirubin.
- Jaundice—a syndrome characterized by hyperbilirubinemia and deposition of bile pigment in the skin, mucous membranes and sclera with resulting yellow appearance of the patient.
- Pallor—absence of skin coloration.
- Respiratory distress—inability to breathe.
- Petechiae—a pinpoint, nonraised , perfectly round, purplish red spot caused by intradermal or submucosal hemorrhage.
- Purpura—purplish or brownish red discoloration of the skin caused by hemorrhage into the tissues.
- Hydrops fetalis—gross edema of the entire body, associated with severe anemia, occurring in erythroblastosis fetalis.
- Death—cessation of life before birth (stillborn) may occur in utero or shortly after birth.

### PREVENTION

Gestation alloimmunization with anti-D in D-negative mothers can be prevented by the use of Rh immune globulin (RhIG). Several theories exist to the reason for the immunosuppressive effect of RhIG. One theory is that it results from an interference with antigen recognition during the induction phase of the primary immunization. Other theories are blocking, immune clearance and immunosat, a feedback mechanism. Scientists have not been able to prove or agree upon any theory for the immunosuppressive effect of RhIG.

RhIG is a formulation prepared from the plasma of humans sensitized with anti-D and is processed to make it a viral free blood derivative. One vial contains 300 µg of anti-D, which will protect against 30 mL of Rh-positive whole blood or 15 mL of Rh-positive red blood cells. A reduced dose or microdose, approximately 50 µg RhIG, which is protective for up to 2.5 mL of Rh-positive fetal red cells, is available; however, because of fears of miscalculating the length of pregnancy and undertreatment, the full dose is usually administered.

It is recommended that RhIG be given at 28 weeks of gestation and within 72 hours of delivery of an Rh-positive infant. The amount of fetomaternal hemorrhage is estimated after delivery by an initial screening test, fetal screen rosette test, and if positive, a quantitative test, the Kleihauer-
Betke acid elution test is performed. RhIG is also recommended for any obstetrical intervention or maternal abdominal trauma in the mother who is Rh negative.