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# Hemolytic Disease of the Newborn

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**Abstract**

Hemolytic disease of the newborn (HDN), with high potential for increased fetal loss is less common now, due to the universal screening for iso-sensitization and also because of appropriate use of antenatal anti-RhD antibody prophylaxis. There are other non-RhD antibodies that can cause HDN. In US, we occasionally encounter a highly sensitized fetus with significant morbidity and mortality. In utero RBC transfusions and Intravenous Immunoglobulin (IVIG) therapy for such an infant are effective to some extent, in the management of HDN. Partial exchange transfusions (immediately after the delivery) and double volume exchange transfusions are rarely but still, needed as rescue modes.

**Keywords:** Hemolytic disease; Erythroblastosis fetalis; Rhesus allo-immunization; Immune hydrops

## Background

The phrase Hemolytic disease of the newborn (HDN) was originally used to describe "Erythroblastosis fetalis" due to Rh (D) incompatibility. It was one of the major causes of fetal loss and death among newborn babies in 1960s and 1970s. HDN can be also caused by non-RhD antibodies. This short review article is mainly focusing on RhD sensitization. It includes a review of historical perspective, pathophysiology of RBC antigen iso-sensitization, hydrops fetalis, clinical presentation, and management of HDN.

## History/Epidemiology

In 1609, a French midwife first described HDN, in a set of twins—one baby was markedly edematous and died soon after birth, the second baby developed jaundice and died several days later [1]. It was not until the 1950s that the underlying cause of HDN was explained [1]. This condition is secondary to an incompatibility between the blood types of the mother and fetus. When fetal red blood cells (RBC) carrying antigens acquired from the father, are exposed to maternal red cells that don't carry those antigens, it results in sensitization of the mother, leading to production of antibodies. Those maternally produced Immunoglobulin-G (IgG) antibodies pass trans-placentally and attack fetal RBCs resulting in hemolysis of the fetal RBCs. That can lead to severe anemia, congestive heart failure, hydrops/erythroblastosis or even death.

During 1960s, in USA and UK, trials showed that giving therapeutic antibodies to women during their pregnancy largely decreased the incidence of HDN, by removing the antibodies that cause HDN [1]. By the 1970s, regular prenatal care included screening of all expectant mothers for risk of developing HDN. A preventive strategy evolved, that led to a dramatic decrease in the incidence, severity and mortality of HDN. The World Health Organization (WHO) technical report in 1971 recommended, that a dose of 25 mcg (125 IU) of anti-D immunoglobulin G (IgG) should be given intramuscularly, for every 1 mL of fetomaternal hemorrhage of Rh-positive packed RBCs or 2 mL of whole blood [2]. In 1998, this recommendation was reinforced by the American Association of Blood Banks and the American College of Obstetrics and Gynecologists with inclusion of prophylaxis at 28 weeks' gestation [3].

## Rh D Antigen and Iso-sensitization

The most immunogenic RBC antigens belong to Rhesus blood group D, followed by c and E. Hemolytic disease of fetus can be also caused by Kell antigen sensitization. Kell antigen can cause hypo-proliferation of erythroid precursors leading to severe anemia. Other Non-RhD antibodies include Rhesus-c, Colton, Diego, Duffy etc. HDN does not usually affect first pregnancy.

All Rh-D negative pregnancies of Rh-D positive partners should be screened early, at the first prenatal visit, for RBC sensitization. Antenatal prophylaxis of anti-D should be offered at the beginning of 3rd trimester and at term. In high risk pregnancies, irrespective of the offending antibody, antenatal management should be coordinated in a specialized center with expertise in the noninvasive ultrasonographic assessment of fetal anemia, consisting of Doppler interrogation of the fetal middle cerebral artery peak systolic velocity, and detailed assessment of the fetal anatomy and placenta 3. Thorough laboratory evaluation of the mother, father, and fetus/neonate is crucial for the management of HDN. Invasive fetal assessment using amniocentesis, fetal blood sampling (per-umbilical blood sampling- PUBS) with the capability of intrauterine transfusion of appropriate blood products, is a must in caring for such pregnancies. Finally, such preterm or term neonate will require care in a specialized Neonatal ICU.

The exposure of the Rh-negative mother to Rh-positive red cells occurs as a result of asymptomatic fetomaternal hemorrhage during pregnancy. Fetomaternal hemorrhage has been documented in 7%, 16%, and 29% of mothers during their first, second and third trimesters, respectively. Risk is also increased in pregnancies complicated by placental abruption, spontaneous or therapeutic abortion, and toxemia, as well as after cesarean delivery and ectopic pregnancy.

The Rh antigens are inherited as a linked group of two genes, RHD and RHCE, located on chromosome 1. Rh negative or positive typing is based on the expression of the major D antigen on the RBC (RBC also express C or c and E or e antigens). Even though, Rh negative geno type is noted in 14.4% of whites and 5.5% of African Americans, not all Rh negative women develop antibodies [4]. So, only a small number of pregnancies are affected. The peripheral blood smear may show anemia, reticulocytosis and macrocytosis. Microspherocytes are not seen in Rh disease (present in ABO incompatibility). A direct antiglobulin (Coombs) test will be positive for anti-D IgG.

## Clinical Manifestations

HDN secondary to RhD antigen can cause significant hemolysis resulting in severe anemia with marked jaundice, heart failure with markedly increased central venous pressure, hepatosplenomegaly, portal vein obstruction, ascites, pleural and pericardial effusions, marked generalized edema (anasarca) , ultimately leading to hydrops and even death of the fetus [5].

### Management of Neonate affected by Erythroblastosis/ Hemolytic disease of the Newborn

Reinforcing earlier statement, there should be a coordinated effort between the referring Obstetrician or Family Physician and the Perinatal center team (Maternal Fetal Medicine specialist, high risk OB staff, Neonatologist with specialized Neonatal team, Maternal transport team and the Blood Center) to deliver the infant at a Level IV Neonatal ICU. Many perinatal centers have fetal anomaly (multi-discipline) committees. Individualized delivery plans are developed by these teams, very early during such complex pregnancies.

Antenatal consultations with a Neonatologist is strongly recommended to provide information to the family, about the expected morbidity, mortality, potential immediate and long term complications, expected procedures, potential length of stay etc.

The delivery of such complex babies needs to be attended by an experienced Neonatologist and a specialized neonatal team. Immediate intubation and positive pressure ventilation, followed by the drainage of pleural cavities (needle aspiration and chest tube placement) and abdominal paracentesis (if needed) are essential for hydropic babies. Frequently, partial exchange transfusion (with O negative blood ordered prior to the delivery), needs to be done without delay in the delivery room (or adjacent room). Its purpose is to raise the hematocrit from teens to mid to high 20s (or increase by approximately 10%). Because of the potential for sudden fluid shift, central venous pressure (CVP) needs to be monitored closely, as it can increase suddenly during the procedure.

Immediate intensive phototherapy is a must, in addition to close monitoring of total and direct bilirubin, hematocrit, serum protein and albumin along with liver and renal chemistry panels. Such babies may need more than one double volume exchange transfusion. It is beyond the scope of this article to discuss details of these procedures [6].

Another evidence based therapy is the use of Intravenous Immunoglobulin (IVIG) in doses of 0.5-1 g/kg in a single or multiple dose regimen, shown to effectively reduce the need for exchange transfusion [7].

### Management of mother with rhesus alloimmunization

All pregnant patients need to undergo an antibody screen at the first prenatal visit. If there is no anti-D alloimmunization in RhD-woman, in US it is recommended to give 300 micrograms of RhIG IM at 28 weeks of gestation (reduces the incidence of alloimmunization from 2% to 0.1%). Some experts recommend a second dose at 40 weeks' gestation. Fifteen to 20% of patients that received RhIG at 28 weeks will have very low titers at term. In US, if umbilical cord shows RhD+ baby, it is recommended to give 300 micrograms of RhIG IM within 72 hours of delivery.

Maternal management also includes maternal antibody determination, in vitro tests, fetal blood typing by Genetics (amniocentesis), ultrasound directed per-umbilical fetal blood sampling (PUBS, cordocentesis, or funipuncture), Intrauterine transfusion, Plasmaphresis, Intravenous-immunoglobulin, antenatal phenobarbital therapy etc. Antenatal phenobarbital therapy is associated 75% reduction in the need for exchange transfusions etc [8]. Current management of severely affected cases of HDFN includes in utero transfusions (IUT) of RBC approximately every 3 weeks, aiming to maintain the fetal hemoglobin level, repeated until the baby can be safely delivered. This could be as many as 4 to 6 in utero transfusions starting from 20 weeks of gestation until 36 weeks of gestation [5]. Treatment with Intravenous immunoglobulin (IVIG) did not appear to modify the disease severity. There was no reduction in the frequency or volume of intrauterine transfusions, the severity of hemolysis, or the development of hydrops fetalis [9]. When treated with IUT appropriately, fetuses with severe hydrops showed no increased risk of neurodevelopmental abnormalities [10].

A recent study showed some women can have multiple antibodies, assumed to be secondary to sensitization from different antigens. In such situations, women with combinations of red blood cell antibodies are more likely to develop significant hemolytic disease of the fetus and newborn than those with single antibodies, especially in the presence of anti-(Rh)D. This pathophysiology may suggest a more aggressive immune response in women who develop more than 1 red blood cell antibody [11].

## Conclusion

Rhesus Alloimmunization and Hemolytic disease of the newborn are rare, but still exist. Because of the need for close monitoring, required expertize in various infrequently done procedures, rarity of the condition and complexity of the management, these pregnancies need to be followed at a Perinatal Center. A coordinated, well planned and executed effort between the Perinatal center and the community health care team is essential for the optimal outcome of such pregnancies. It is also essential to realize the importance and effectiveness of Universal screening.

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