RH BLOOD-GROUP INCOMPATIBILITY

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1. Core Definition and Pathophysiology

Rh blood-group incompatibility, sometimes referred to as Rh disease or Rhesus incompatibility, is an alloimmune condition that arises when an Rh-negative individual is exposed to Rh-positive red blood cells, triggering an immune response. This phenomenon is most clinically significant in obstetrics, where an **Rh-negative mother** carries an **Rh-positive fetus**. The incompatibility centers on the D antigen, a crucial protein located on the surface of red blood cells (RBCs). An individual is deemed Rh-positive if this D antigen is present and Rh-negative if it is absent. The core pathological mechanism involves the production of maternal antibodies, specifically anti-D immunoglobulin G (IgG), which are capable of crossing the placenta and targeting the fetal RBCs for destruction, leading to hemolysis.

The initial exposure, or sensitization event, typically occurs during delivery, placental separation, ectopic pregnancy, abortion, amniocentesis, or trauma, which allows fetal red blood cells to enter the maternal circulation. Because this primary exposure often happens late in the pregnancy or at birth, the first Rh-positive fetus is usually unaffected or only mildly affected, as the maternal immune system takes time to mount a significant response. This initial response produces IgM antibodies, which generally cannot cross the placenta. However, subsequent exposure to Rh-positive blood in future pregnancies triggers a rapid and robust secondary immune response, yielding high concentrations of IgG antibodies. It is these smaller, transplacental IgG antibodies that constitute the primary threat, as they bind to the D antigens on fetal RBCs, initiating destruction via splenic macrophage activity, resulting in **Hemolytic Disease of the Fetus and Newborn (HDFN)**.

If left untreated or undiagnosed, the persistent destruction of fetal red blood cells results in severe fetal anemia. To compensate for this rapid loss, the fetus attempts to accelerate RBC production (erythropoiesis), leading to an overabundance of immature red blood cells (erythroblasts) in the circulation--hence the historical term **Erythroblastosis Fetalis**. This chronic anemia can lead to heart failure, widespread edema, ascites, and pleural effusions, a condition known as **hydrops fetalis**, which is often fatal. Even if the fetus survives, severe hemolysis post-delivery can result in high levels of bilirubin, leading to kernicterus, a devastating form of brain damage caused by bilirubin deposition in the central nervous system.

2. Genetics of the Rh Blood Group System

The Rh blood group system is one of the most complex and clinically important human blood group systems after the ABO system. It is governed by two closely linked genes located on the short arm of chromosome 1: the **RHD gene** and the **RHCE gene**. The RHD gene determines the presence or absence of the D antigen, which is the primary antigen responsible for severe Rh incompatibility. Individuals who inherit at least one copy of the functional *RHD* gene (DD or Dd) are Rh-positive, while individuals who inherit two non-functional copies (dd) are Rh-negative.

The prevalence of Rh status varies significantly across global populations. Approximately 85% of people of European descent are Rh-positive, while Rh-negativity is much less common in populations of African and East Asian descent. This genetic distribution is critical when assessing maternal risk; for instance, the risk of an Rh-negative mother being sensitized is higher in Caucasian populations simply due to the higher prevalence of Rh-positive partners. Genetic counseling often involves analyzing the paternal Rh genotype. If the father is heterozygous (Dd), there is a 50% chance the fetus will be Rh-positive; if the father is homozygous (DD), the fetus will inevitably be Rh-positive, placing the mother at risk if prophylaxis is not administered.

Understanding the genetics also involves recognizing variants such as the **Weak D** (formerly Du) phenotype. Individuals classified as Weak D express the D antigen, but in a modified or reduced form. While historically treated differently, most individuals with Weak D phenotypes are now considered Rh-positive, particularly in transfusion medicine. However, complications arise when an Rh-negative patient receives blood from a Weak D donor, or, conversely, when a Weak D mother is capable of producing anti-D antibodies if exposed to standard Rh-positive cells, although this maternal sensitization risk is significantly lower than for truly Rh-negative individuals.

3. Clinical Manifestations and Diagnosis in Pregnancy

Diagnosis of Rh incompatibility begins with initial prenatal screening. All pregnant women undergo ABO and Rh typing, along with an antibody screen (Indirect Coombs Test). If the mother is Rh-negative, the antibody screen is crucial. A negative screen indicates the mother has not yet been sensitized. If the screen is positive, indicating the presence of anti-D antibodies, the titer level must be monitored throughout the pregnancy. A critical titer--typically 1:16 or greater--indicates a significant risk of HDFN requiring specialized fetal surveillance.

Once high-risk status is established, fetal assessment shifts to non-invasive monitoring. The gold standard for assessing fetal anemia is measuring the peak systolic velocity (PSV) of the fetal **middle cerebral artery (MCA-PSV)** using Doppler ultrasound. In an anemic fetus, the blood viscosity decreases, causing blood flow velocity in the MCA to increase. An MCA-PSV measurement exceeding 1.5 multiples of the median (MoM) is highly predictive of severe fetal anemia, necessitating intervention. This non-invasive method has largely replaced invasive procedures like amniocentesis for measuring bilirubin levels, which carries risks of potentially causing further maternal sensitization.

The manifestations of HDFN in the fetus range from mild anemia, which may be asymptomatic, to severe, life-threatening conditions. In severe cases, the sustained destruction of RBCs causes extramedullary hematopoiesis, where blood cells are produced in organs like the liver and spleen, leading to hepatosplenomegaly. When the fetal capacity to produce new cells and compensate for hemolysis is overwhelmed, fetal anemia progresses to high-output cardiac failure and, ultimately, hydrops fetalis. Postnatally, the primary clinical concern in neonates is **hyperbilirubinemia**, caused by the breakdown of hemoglobin released from lysed red cells. Unconjugated bilirubin can cross the blood-brain barrier, leading to kernicterus, characterized by neurological deficits, hearing loss, and cerebral palsy.

4. Prevention: The Role of Rh Immune Globulin (Rhogam)

The clinical management of Rh incompatibility was revolutionized by the introduction of **Rh immune globulin (Rho(D) immune globulin)**, commonly known by the trade name **Rhogam**. Rhogam is a purified preparation of IgG anti-D antibodies derived from human plasma. Its use has dramatically reduced the incidence of severe HDFN from approximately 1% in all pregnancies to less than 0.1%.

The mechanism of action of Rhogam is based on passive immunity and immune suppression. When administered to an Rh-negative mother, the exogenous anti-D antibodies attach to any fetal Rh-positive red blood cells that may have entered the maternal circulation during the sensitizing event. These coated fetal cells are then rapidly cleared by the maternal reticuloendothelial system (e.g., the spleen) before the mother's own immune system can recognize the D antigen and mount a primary, long-lasting immune response. Effectively, Rhogam fools the maternal immune system into believing that the Rh antigen exposure has not occurred, thereby preventing the formation of permanent anti-D memory B cells.

The prophylactic protocol for Rhogam involves two primary administrations. The first dose is typically given antenatally around 28 weeks of gestation, providing coverage during the third trimester when the risk of microtransfusion increases. The second, and often more critical, dose is administered postnatally, generally within 72 hours after delivery, but only if the neonate is confirmed to be Rh-positive. Rhogam is also mandated following any potentially sensitizing events throughout pregnancy, including amniocentesis, chorionic villus sampling (CVS), abdominal trauma, external cephalic version, miscarriage, or therapeutic termination. Strict adherence to this prophylactic regimen is the cornerstone of modern obstetrical care for Rh-negative women.

5. Therapeutic Interventions for the Affected Fetus and Neonate

If prevention fails and the maternal anti-D titer reaches critical levels, requiring intervention, treatment modalities focus on mitigating anemia and managing hyperbilirubinemia. For the fetus suffering from severe anemia diagnosed via MCA-PSV, the primary treatment is the **intrauterine blood transfusion (IUT)**. This invasive procedure involves transfusing Rh-negative packed red blood cells directly into the fetal circulation, usually into the umbilical vein (intravascular transfusion). IUTs replenish the fetal red cell mass, correct anemia, and interrupt the cycle that leads to hydrops fetalis, often requiring repeated transfusions every 1 to 4 weeks until the fetus reaches maturity and can be delivered safely.

For the newborn suffering from HDFN, treatment is immediately focused on controlling hyperbilirubinemia. **Phototherapy** is the initial non-invasive treatment, using blue light wavelengths to convert unconjugated bilirubin in the skin into water-soluble isomers that can be excreted in the urine and bile. However, if bilirubin levels rise rapidly or reach neurotoxic levels despite intensive phototherapy, an **exchange transfusion** is necessary. This procedure involves systematically removing small volumes of the neonate's blood and simultaneously replacing them with donor Rh-negative blood. The exchange transfusion achieves two critical goals: it removes the circulating anti-D antibodies and sensitized red cells, and it dramatically reduces the serum bilirubin concentration, preventing kernicterus.

The decision to deliver an affected fetus is a careful balance between the risks of prematurity and the severity of the hemolytic disease. If IUTs successfully manage the condition, delivery may be timed closer to term (37-38 weeks). In cases where the condition is mild or moderate, a timely delivery coupled with prompt postnatal management (phototherapy) can ensure a favorable outcome, highlighting the collaborative effort required between obstetricians, neonatologists, and hematologists in managing this complex immunological condition.

Further Reading

Rh Blood Group System (Wikipedia)
Rh Incompatibility (MedlinePlus)
Hemolytic Disease of the Fetus and Newborn (StatPearls)