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Original Article

Hemolytic Disease of The Newborn

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ABSTRACT

Hemolytic disease of the newborn (HDN), or erythroblastosis fetalis, primarily impacts rhesus-positive fetuses born to rhesus-negative mothers. The condition arises when maternal antibodies, formed after alloimmunization due to rhesus or ABO blood type incompatibility, attack fetal red blood cells. Historically, HDN was associated with a fetal death rate of about 1% in pregnancies. However, advancements in immunoprophylactic treatments have significantly improved management and outcomes when the condition is diagnosed early. Diagnosis involves a comprehensive assessment, including patient history, physical exams, serological tests, and imaging, such as pelvic ultrasound. Preventative measures, like administering intravenous immunoglobulin (IVIG) to unsensitized Rh-negative mothers, are crucial. Understanding potential complications, particularly severe hyperbilirubinemia, is also essential for effective treatment. With ongoing research, the understanding of HDN continues to evolve, leading to better management strategies and outcomes in clinical practice. This review discusses the etiology, diagnosis, and current management approaches for HDN, highlighting recent findings and future directions for research. Since the identification of the Rh blood group system in 1940, there has been an improved understanding of hemolytic disease of the fetus and newborn (HDFN).

Keywords: fetomaternal hemorrhage, hemolysis, immunoprophylaxis, Hemolytic Disease of the Newborn (HDN), Direct Coombs Test, ABO Incompatibility, Rh Incompatibility

INTRODUCTION

Hemolytic disease of the newborn (HDN) is a medical condition where the red blood cells of a fetus are destroyed by maternal IgG antibodies that target antigens inherited from the father.The primary issue related to Rh incompatibility is hemolytic disease of the newborn (HDN), which can develop during pregnancy. Typically, there is no direct mixing of maternal and fetal blood. However, if some Rh+ blood from the fetus enters the bloodstream of an Rh− mother through the placenta, the mother will start producing anti-Rh antibodies. Since the most significant chance of fetal blood entering the maternal circulation is during delivery, the firstborn child is usually unaffected. If the mother becomes pregnant again, her anti-Rh antibodies can cross the placenta and reach the fetus. If the fetus is Rh−, there's no concern, as Rh− blood lacks the Rh antigen. Conversely, if the fetus is Rh+, this can lead to agglutination and hemolysis due to the incompatibility between maternal and fetal blood. An injection of anti-Rh antibodies, known as anti-Rh gamma globulin (RhoGAM®), can be administered to prevent hemolytic disease of the newborn (HDN). Rh− women should receive RhoGAM® prior to delivery and shortly after each delivery, miscarriage, or abortion. These antibodies attach to and neutralize fetal Rh antigens before the mother's immune system has a chance to react by producing its own anti-Rh antibodies. HDN is estimated to affect 3 to 8 individuals per 100,000 patients each year. Before the introduction of anti-D prophylaxis, it caused fetal loss in 1% of pregnancies. The occurrence of HDN is closely linked to the inheritance pattern in females that leads to the absence of the Rhesus (D) antigen, and its incidence varies by ethnicity. Research shows that white individuals have the highest prevalence,

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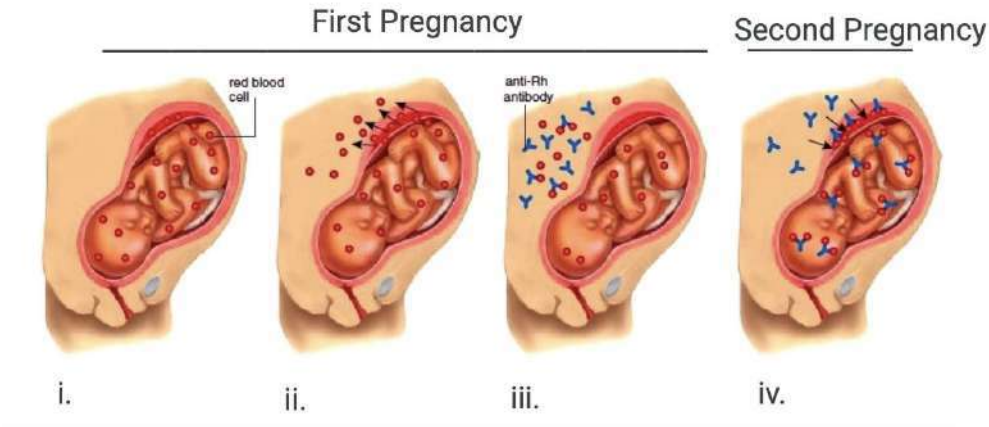
while Asians and American Indians have the lowest, as shown in Table 1. Additionally, among the various Rh antigens, the D antigen is the most immunogenic. It's estimated that around 10% of pregnant white women are Rh incompatible Due to its high prevalence and characteristics, HDN has been the subject of extensive research, with new studies emerging annually that shed light on various aspects of the disorder. This review summarizes HDN in terms of its etiology, diagnosis, and management, incorporating the latest findings from 2021 and discussing trends and prospects to support evidence-based medical practice and further research.

Hemolytic Disease of the Newborn [Erythroblastosis Fetalis] encompasses three main clinical forms:

(a) hydrops fetalis,
(b) severe jaundice in newborns, and
(c) hemolytic anemia in newborns.

The likelihood of severe hemolytic disease of the fetus and newborn (HDFN) is influenced by various factors, such as the subclass of IgG, the specificity and titer of the antibodies, and how much of the relevant antigen is present on the fetal red blood cells. While anti-Rh17 antibodies are primarily associated with severe cases of HDFN, there have been instances where the condition was mild.



Development of Hemolytic Disease of the Newborn (HDN)

(a) At birth, a small amount of fetal blood typically leaks into the mother's bloodstream. This can lead to issues if the mother is Rh− and the baby is Rh+, having inherited the Rh antigen allele from the father.
(b) Upon encountering the Rh antigen, the mother's immune system produces anti-Rh antibodies.
(c) In a subsequent pregnancy, these maternal antibodies can cross the placenta into the fetal blood. If the second fetus is Rh+, the resulting antigen-antibody reaction causes agglutination and hemolysis of the fetal red blood cells, resulting in HDN

Etiology :

Although signs in fetuses and newborns were observed as early as the 17th century, it wasn't until 1939 that Levine and Stetson documented a transfusion reaction after a husband's blood was given to a postpartum woman. They suggested that the mother had become sensitized to the father's antigen via fetomaternal hemorrhage, later identified as Rh(D). Hemolytic disease of the fetus and newborn (HDFN) occurs when maternal antibodies destroy fetal red blood cells (RBCs). Only immunoglobulin G (IgG) antibodies can cross the placenta; other types, like IgA and IgM, cannot. While most IgG antibodies target bacterial, fungal, and viral antigens, in HDFN, the antibodies attack antigens on fetal RBCs inherited from the father. Levine, Katzin, and Burnham (15) proposed a theory regarding the pathogenesis of erythroblastosis fetalis, which involves two key processes:

1. The mother's iso-immunization occurs due to a dominant hereditary blood factor from the fetus inherited from the father, leading to the production of intragroup agglutinins.

2. These agglutinins then continuously pass from the mother's circulation through the placental barrier, where they affect the fetal blood.

History:

In 1609, a French midwife reported the first known case of hemolytic disease of the fetus and newborn (HDFN) involving twins, one of whom died from hydrops and the other from jaundice by day three. By the late 1800s, around 70 similar cases were documented. It wasn't until 1932 that researchers identified severe hemolysis and extramedullary erythropoiesis as causes of hydrops, jaundice, and kernicterus, although the root cause was still unclear. Eventually, it was discovered that maternal antibodies against fetal red blood cells cross the placenta, leading to hemolysis, with initial beliefs in 1938 incorrectly attributing the antibodies' target to fetal red blood cells. Shortly after this, in 1940, Landsteiner and Wiener defined the Rh blood group system, which clarified the pathogenesis of HDFN significantly. There are indications that HDFN was somewhat recognized long before the historical events of the English monarchy mentioned earlier, and it is believed that HDFN may have contributed to the events that sparked the English Reformation in the sixteenth century. In 1509, Katherine of Aragon married Henry VIII, and they had six children, five of whom died either in utero or shortly after birth. Only one girl survived, and because it was believed she couldn't produce a living male heir, Henry VIII sought to annul his marriage. This request led to conflicts with the Pope, but ultimately the marriage was annulled by the Archbishop of Canterbury, resulting in England's split from Rome. If the deaths of these children were indeed due to HDFN, as suggested by Rosse history, then HDFN has profoundly influenced both English and Roman history as we know it today. Some researchers suggest that the medical literature on HDFN dates back even further than previously thought. Hippocrates, often known as the Father of Medicine, described a condition called fetus carnosus, which medical historians believe may have represented fetal hydrops as early as 400 BC. It wasn't until 1940 that Austrian physician and immunologist Karl Landsteiner, along with American immunohematologist Alexander Wiener, discovered and described the Rh blood group system, in addition to the already known ABO system, by immunizing guinea pig and rabbit cells. In 1941, another American immunohematologist, Philip Levine, demonstrated that the RhD antigen was the immune target for the IgG response observed in erythroblastosis fetalis, as well as the ability of the antibody to cross the placenta. This research enhanced the understanding of Rh-HDFN and also contributed to the broader physiological understanding of all types of HDFN. Levine continued his research in this field, and in 1956, he demonstrated that the risk of sensitization to the RhD antigen is lower when the fetus is also ABO incompatible with the mother, particularly if the mother has type O blood. Any fetal cells that enter the maternal circulation are quickly destroyed by the strong and naturally occurring maternal anti-A and/or anti-B antibodies, which decreases the chance of maternal exposure to the RhD antigen and subsequent sensitization. In 1961, English medical researcher Ronald Finn made two significant discoveries. He demonstrated that fetal red blood cells circulate in the maternal system of RhD-negative mothers—and indeed, in all mothers. He then showed that administering passive anti-D immunoglobulin (IgG) sped up the clearance of RhD-positive red blood cells in RhD-negative male volunteers. In 1963, American obstetrician Vincent Freda created the first specific anti-D immunoglobulin preparation. That same year, German physician Schneider demonstrated similar effects in nonpregnant RhD-negative female volunteers who received passive anti-D to prevent sensitization after being infused with RhD-positive cells. This research laid the groundwork for preventing sensitization in pregnant women and has saved millions of lives worldwide since then. While there hasn't been any immunological advancement in prophylaxis for other types of HDFN, significant progress in neonatal medicine over the past century has resulted in increased survival rates and reduced long-term morbidity for babies born with all forms of HDFN.

Pathophysiology of haemolytic disease of the fetus and newborn :

Maternal alloimmunization in hemolytic disease of the newborn (HDFN) can occur from incompatible blood transfusions or fetomaternal hemorrhage. IgG antibodies cross the placenta, leading to fetal red blood cell destruction, resulting in anemia. The fetus may develop compensatory mechanisms, but these can be insufficient, causing cardiomegaly and fetal hydrops. Elevated bilirubin levels from red blood cell breakdown can overwhelm the newborn's immature liver, leading to severe hyperbilirubinemia and kernicterus, which may cause long-term neurological

damage. Early detection of maternal alloantibodies allows for monitoring and interventions, such as intrauterine transfusions and postnatal treatments like phototherapy to prevent complications. A structured screening program is crucial for identifying at-risk pregnancies and managing HDFN effectively. Once Rh (D) alloimmunization occurs, maternal IgG antibodies can cross the placenta and bind to the Rh (D) antigen on fetal red blood cells, leading to their destruction in the fetal spleen and resulting in hemolytic anemia. This anemia triggers increased erythropoiesis, prompting the bone marrow to produce more red blood cells. If the anemia is severe, the bone marrow may be unable to keep up with demand, leading to extramedullary erythropoiesis in the liver and spleen, which can cause hepatosplenomegaly. Additionally, this process results in immature erythroblasts being released into the bloodstream.

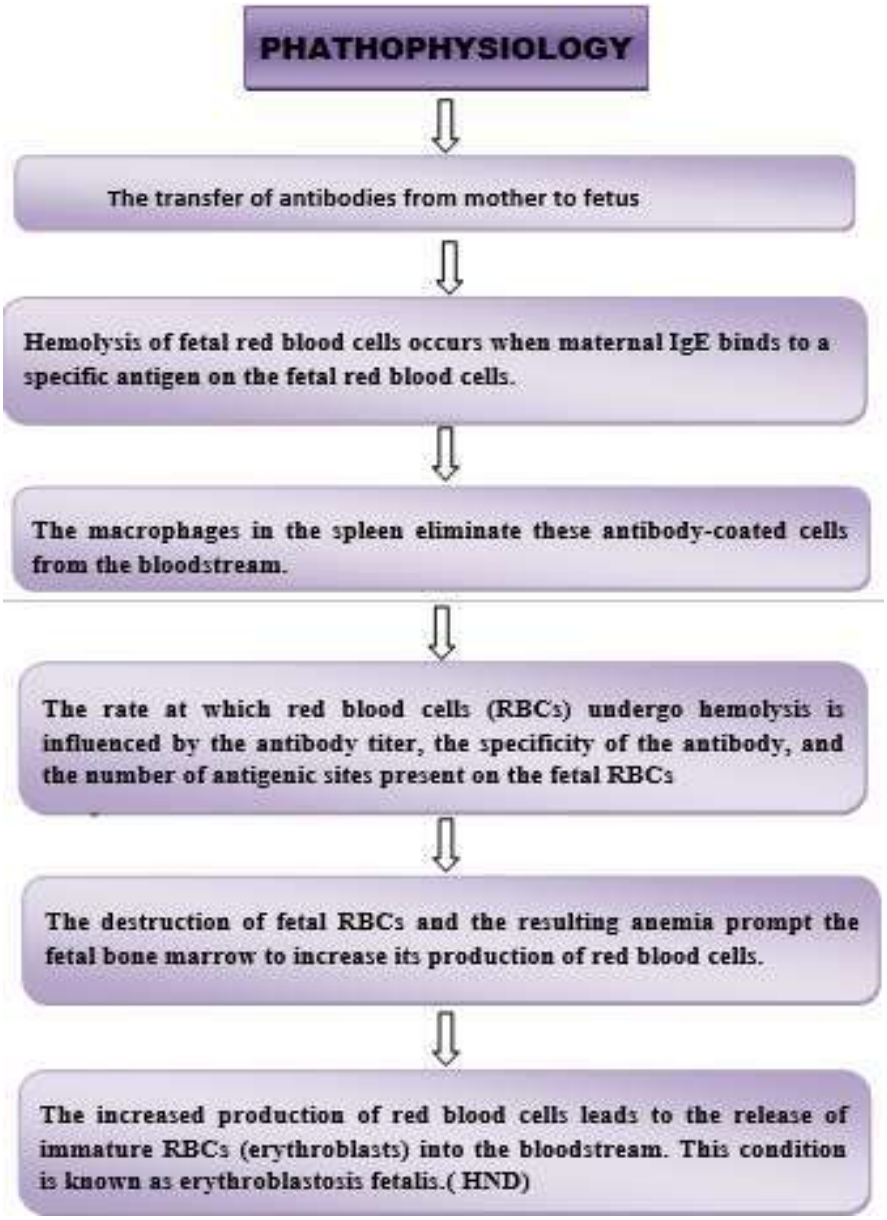


Figure: Pathophysiology of Hemolytic newborn disease

Causes of hemolytic newborn disease:

A] Typical causes of hemolytic disease in newborns:

1- Antibodies from the Rh system

2- Antibodies from the ABO system

B] Less common causes:

1- Antibodies from the Kell system

C] Uncommon causes:

1- Antibodies from the Duffy system
2- Antibodies from the MNS and s systems

D] Not associated with hemolytic disease of the newborn:

1- Antibodies from the Lewis system
2- Antibodies from the P system

E] Differential Diagnoses:

1]- Acute Anemia
2]- Atrial Flutter
3]- Cardiac Tumors
4] Cytomegalovirus Infection
5]-Galactose-1-Phosphate Uridyltransferase Deficiency
6]-Hydrops Fetalis
7]- Hypothyroidism
8]- Parvovirus B19 Infection
9]- Syphilis
10]- Toxoplasmosis
11]- Tyrosinemia

Symptoms of Hemolytic Disease of the Newborn:

1] During pregnancy, symptoms can include:

1**]-** Amniocentesis may reveal yellow-tinged amniotic fluid containing bilirubin.
2]- An ultrasound of the fetus might indicate an enlarged liver, spleen, or heart, as well as fluid accumulation in the fetus's abdomen.

2] After birth, symptoms may include:

1]- Pale skin due to anemia.
2]- Jaundice, characterized by yellowing of the amniotic fluid, umbilical cord, skin, and eyes. While the baby might not appear yellow immediately after birth, jaundice can develop quickly, typically within 24 to 36 hours.
3]- An enlarged liver and spleen in the newborn.
4]- Severe edema (swelling) throughout the body in babies with hydrops fetalis, along with extreme paleness.
5]- Breathing difficulties.
6]- Complications from hemolytic disease of the newborn can vary from mild to severe.

3] During pregnancy:

1]- Mild anemia, hyperbilirubinemia, and jaundice may occur, as the placenta can help remove some bilirubin, but not all of it.
2]- Severe anemia may lead to the enlargement of the liver and spleen. When these organs and the bone marrow are unable to compensate for the rapid destruction of red blood cells, it results in severe anemia that can affect other organs.
3]- Hydrops fetalis occurs when the baby's organs cannot manage the anemia, leading to heart failure and significant fluid accumulation in the baby's tissues and organs. A fetus with hydrops is at a high risk of still birth.

4] After birth:

1]- Severe hyperbilirubinemia and jaundice occur when the baby's liver cannot process the excess bilirubin from red blood cell breakdown. This can lead to an enlarged liver and ongoing anemia.
2]- Kernicterus is the most severe form of hyperbilirubinemia, resulting from bilirubin accumulation in the brain. It can cause seizures, brain damage, deafness, and potentially death.

Laboratory diagnosis of hemolytic disease of the newborn :

The diagnosis of Erythroblastosis Fetalis relies on three factors:

1. Evidence of maternal isoimmunization to Rh positive fetal blood through the detection of anti-Rh antibodies in the mother.
2. Confirmation that maternal antibodies have crossed the placenta to the fetus.
3. Identification of clinical and hematological signs indicating excessive blood destruction and regeneration in the newborn.

Prenatal Testing :

1] Prenatal testing is conducted to identify the presence of IgG antibodies that may lead to hemolytic disease in newborns. This helps in recognizing, monitoring, and providing timely treatment for the infant.
2] To identify which women should receive Rhesus Immune Globin (RhIg) to prevent the formation of anti-D antibodies, maternal antibody levels serve as an effective measure of the severity of hemolytic disease in newborns.

3] Ultrasound is used to identify organ enlargement or fluid accumulation in the fetus. It allows for the observation of internal organ function and the evaluation of blood flow in different vessels.
4] Amniocentesis is performed to assess the bilirubin levels in the amniotic fluid.
5] It involves taking a sample of blood from the fetal umbilical cord during pregnancy to test for antibodies, bilirubin, and anemia in the fetus.

Father Testing:

1] Investigative tests on the father are based on the maternal antibodies present. If the mother has anti-D and Rhesus typing with anti-D, -C, -E, -c, and -e, these tests help determine the likely Rhesus genotype of the father. This information is used to assess the probability of the fetus being Rhesus positive and at risk for hemolytic disease of the newborn.
2] If the initial Rhesus typing shows D-negative, perform a weak D test. For fathers who are D-positive, their likely Rhesus genotype can be assessed using serological tests, specifically DCEce typing, to determine whether they are probably homozygous or heterozygous for the D antigen.
3] When testing the father, determine his phenotype for any clinically significant maternal antibodies, including both the corresponding antigen and its antithetical antigen (for example, K and k).

Molecular genotyping:

1] Molecular genotyping methods are available for typing various blood group loci, including Rhesus (RHD and RHCE), Kell (K and k), Duffy (Fya and Fyb), and Kidd (Jka and Jkb). In prenatal testing programs, molecular typing can identify the Rhesus type of the mother, father, and fetus. This is especially important if the mother has anti-D or another antibody associated with hemolytic disease of the newborn. DNA-based techniques are commonly employed in these situations.
2] For women who test as weak D in serological assays, it's important to assess the mother's Rhesus genotype to determine if she is partial D or weak D.
3]In cases where women have developed anti-D, it's crucial to evaluate the father's Rhesus genotype to ascertain whether fetal monitoring is necessary. Additionally, if the father is heterozygous for Rhesus D or cannot be tested, the Rhesus type of the fetus should also be determined.
4] Fetal blood typing can be performed using fetal DNA obtained from cells collected through amniocentesis or by analyzing cell-free, fetal-derived DNA found in maternal plasma starting at 5 weeks of gestation and beyond.

In cases where the mother has anti-D and the father is D positive, molecular typing can clarify whether the father is homozygous or heterozygous for the but indicating that the fetus should be monitored for hemolytic disease of the newborn. Conversely, if the father is heterozygous for Rhesus D, the fetal Rhesus type should be determined to assess the potential risk for hemolytic disease Rhesus D allele. If the father is homozygous, all of his children will be Rhesus positive, eliminating the need for fetal D testing of the newborn.

Postnatal Testing:

Postnatal testing for hemolytic disease of the newborn involves several diagnostic procedures once the baby is born, including**:**

1] Testing the baby's umbilical cord blood for blood group, Rhesus factor, red blood cell count, and antibodies.
2] Assessing the ABO blood group system (anti-A and anti-B).
3] Evaluating the Rhesus system, which includes Rhesus D, E, e, C, and combinations of antibodies (e.g., anti-Arch and anti-RhE antibodies), as these can be severe.
4] Testing the Kell system for antibodies such as anti-Kell and anti-K1, which are common, as well as rarer antibodies like anti-K2, anti-K3, and anti-K4.
5]Other blood group antibodies, including Kidd, Lewis, Duffy, MN, P, and others, should also be tested on fetal blood or umbilical cord blood**.**
6]The Direct Antiglobulin Test (DAT) is a crucial tool for identifying Hemolytic Disease of the Newborn (HDN) resulting from erythrocyte immunization. The direct Coombs test is employed to confirm whether the fetus or neonate has immune-mediated hemolytic anemia.
7]A full blood count is important, focusing on hemoglobin levels and platelet counts.
8]Peripheral blood morphology often shows increased reticulocytes, and in moderate to severe cases, erythroblasts (nucleated red blood cells) may be present.

9]Biochemical tests for jaundice should measure both total and indirect bilirubin levels.

Testing on maternal blood includes:

1] The Acid Elution technique of the Kleihauer-Betke test or flow cytometry, which can confirm whether fetal blood has entered the maternal circulation and estimate the volume of fetal blood that has crossed over.
2]The indirect Coombs test, which screens the blood of antenatal women for IgG antibodies that could pass through the placenta and potentially lead to hemolytic disease of the newborn.

Treatment:

The prevention and treatment of hemolytic disease of the fetus and newborn (HDFN) has greatly improved since the 1970s, when it was a major cause of perinatal issues. Primary prevention includes administering anti-D immunoglobulin to RhD-negative mothers and careful matching of blood transfusions for women of childbearing age. Secondary prevention involves screening all pregnant women for red cell antibodies to identify and manage at-risk pregnancies early.

1]Antenatal treatment of hemolytic disease:

1]Plasma Exchange:

Plasma exchange, or plasmapheresis, is a recognized therapeutic method for managing red cell alloimmunization by reducing maternal antibody titers. Currently, this treatment is particularly useful in cases of hemolytic disease of the fetus and newborn (HDFN) that develop early in pregnancy (before 20 weeks). The American Society for Apheresis recommended in 2013 that plasmapheresis be considered between the 7th and 20th weeks of pregnancy and continued until intrauterine transfusion (IUT) can be safely performed, typically around 20 weeks of gestation.

2]Absorption of alloantibodies onto red blood cells:

Blood plasma containing antibodies is collected from the patient. These antibodies are then absorbed using specific red blood cells, and the plasma is subsequently returned to the patient. This method was explored by Robinson and Yoshida et al. during the 1980s for a woman who had been immunized against Rh factor**.**

3]Intravenous immunoglobulin administered to the mother

In the last two decades, administering intravenous immunoglobulin (IVIG) to the mother has emerged as one of the alternative strategies for managing severely alloimmunized pregnancies. IVIG is thought to work by saturating FcRn, which may prevent the transfer of anti-D antibodies to the fetus, as demonstrated by Morgan et al. in 1991. Treatment options have included a single dose of 2 g/kg over five days or weekly injections of 1 g/kg, often combined with plasma exchange or intravascular transfusion for the fetus. There is no additional information regarding dosing during the antenatal period.

4] IVIG given to fetus:

Administering IVIG to the fetus did not demonstrate any positive effects.

5] Intrauterine Monitoring:

When a pregnancy is identified as at risk due to a positive or increasing indirect antiglobulin test (IAT), serial Doppler ultrasound measurements of the middle cerebral artery (MCA) velocities are used to assess fetal anemia. If mild anemia is found, ultrasound monitoring continues until the fetus reaches adequate lung maturity or the pregnancy is delivered at term.

If severe anemia is suspected, cordocentesis can be performed to confirm the diagnosis (hematocrit <30% or hemoglobin <10 g/dL). In cases of confirmed severe anemia, an intrauterine transfusion may help prevent the development of a severely ill, hydropic infant. The transfusion uses packed red blood cells (pRBCs) that are negative for the relevant RBC antigen associated with hemolytic disease of the fetus and newborn (HDFN). Additional requirements for the pRBCs include leukodepletion, being from a cytomegalovirus-negative donor, and irradiation to reduce**:**the risk of transfusion-associated graft versus host disease**.**

In 1970, Pontuch identified five strategies to prevent Hemolytic Disease of the Fetus and Newborn (HDFN), which remain relevant today :

1. "Preventing the transfer of fetal red blood cells into the mother's bloodstream and maternal antibodies into the fetus"
2. "Inhibiting antibody production in the maternal bloodstream"
3. "Avoiding sensitization of maternal red blood cells by fetal red blood cells"
4. "Preventing Rh sensitization through the administration of anti-D"
5. "Performing intrauterine transfusions during pregnancy"

6]Induction GvHD:

Induction of GvHD occurs when the immunomodulatory effects from transfusions during intrauterine transfusion (IUT) lead to graft-versus-host disease (GvHD) due to the donor's HLA group.

7]Premature delivery:

Premature labor may be induced, since the transfer of antibodies from the placenta stops after the baby is born.

Postnatal intervention for hemolytic disease:

1] Exchange Transfusion :

The primary objectives of exchange transfusion in cases of hemolytic disease of the fetus and newborn (HDFN) are as follows:

1. By using sedimented red blood cells, it can elevate the hematocrit without increasing the blood volume in a severely affected newborn within the first few minutes of life.
2. It can eliminate antibody-coated cells from the newborn's bloodstream before they undergo hemolysis and lead to bilirubin production.
3. It helps reduce bilirubin levels in the circulating plasma and from extravascular areas, keeping its concentration below thresholds that are generally deemed toxic to tissues, especially those in the central nervous system.

Components Used in Exchange Transfusion:

Red blood cells designated for exchange transfusion must adhere to the following BCSH criteria:

1. Blood Group: Group O or ABO compatible with both maternal and neonatal plasma, and RhD negative (or RhD identical to the neonate).

2. Antigen Compatibility: Negative for any red cell antigens to which the mother has developed antibodies.

3. Cross-Matching : IAT-cross-match compatible with maternal plasma.

4. Age of Red Cells: Must be 5 days old or younger to ensure optimal red cell function and low potassium levels in the supernatant.

5. Anticoagulant and Serostatus: Collected in CPD anticoagulant and should be CMV seronegative.

6. Irradiation: Should be irradiated and transfused within 24 hours post-irradiation. This is crucial if the infant has undergone previous intrauterine transfusions (IUT) and is recommended for all exchange transfusions.

7. Hematocrit Level: Should have a hematocrit between 0.50 and 0.60.

8. Storage Guidelines: Should not be transfused directly from 4°C storage, and care must be taken to prevent overheating of the component.

Fresh Frozen Plasma (FFP):

Red blood cells are suspended in AB plasma to supply plasma proteins, coagulation factors, and albumin. Reconstituted whole blood is created by adding an appropriate amount of FFP to a preservative-free RBC unit, aiming for a hematocrit level of 40–45%. The volume of blood needed for exchange is calculated based on the estimated circulating blood volume of the neonate:

Term Infants: 80–160 mL/kg

Preterm Infants: 100–200 mL/kg

The volume to be exchanged is typically calculated as one-quarter (¼) of the circulating blood volume.

2. Phototherapy :

Phototherapy is an effective treatment for hyperbilirubinemia, as it works by denaturing bilirubin at specific wavelengths. The American

Academy of Pediatrics (AAP) and the National Institute for Health and Care Excellence (NICE) have established guidelines for initiating treatment, taking into account factors such as gestational age, birth weight, and the underlying cause of hyperbilirubinemia.

3] Intravenous Immunoglobulin (IVIG):

IVIG works by blocking the Fc receptor sites on the cells of the reticuloendothelial system, which helps prevent the hemolysis of sensitized cells. It is primarily used for managing ABO hemolytic disease of the fetus and newborn (HDFN) and is less effective in cases of anti-D-mediated HDFN.

4] Other Blood Groups:

Anti-C can occasionally cause hemolytic disease of the newborn (HDN) as severe as that caused by anti-D and is managed in a similar manner. Isolated anti-E is generally not a significant issue; however, when combined with anti-C, it may require treatment.

5] Erythropoietin:

Anemia that appears in the initial weeks of life, referred to as 'late anemia,' affects 71–83% of neonates with hemolytic disease of the fetus and newborn (HDFN) and is marked by reduced erythropoiesis. While administering EPO might help prevent late anemia and decrease the requirement for additional red blood cell transfusions, there is currently insufficient evidence to back this claim.

Alternative:

Various pharmacological agents have been explored as potential treatments for neonatal hyperbilirubinemia. The primary substances of interest include albumin, phenobarbital, metalloporphyrins, zinc, clofibrate, and prebiotics. However, none of these agents is presently advised as standard treatment for hyperbilirubinemia.

1]Albumin:

Albumin is believed to help reduce serum bilirubin levels because it binds to bilirubin. However, well-powered studies demonstrating its clinical benefits are insufficient, and albumin administration is not currently recommended as standard treatment. A small randomized controlled trial in India by Shahian et al. suggested that administering albumin before an exchange transfusion might help decrease total serum bilirubin levels afterward and reduce the duration of phototherapy. In contrast, another randomized controlled trial did not find similar results. The AAP suggests measuring serum albumin levels in neonates with hyperbilirubinemia, considering levels below 3.0 g/dL as an additional risk factor that may lower the threshold for phototherapy. Additionally, serum albumin levels should always be checked if exchange transfusion is being considered, and the bilirubin/albumin ratio should be used to assess the need for transfusions. Overall, albumin supplementation is not recommended.

2]Phenobarbital:

Phenobarbital was initially used in the 1970s to enhance biliary flow. It works by increasing the activity of hepatic uridine diphosphate (UDP)-glucuronosyl transferase (UGT) and promoting bilirubin conjugation, potentially aiding in bilirubin uptake by the liver. A recent randomized clinical trial by Kaabneh et al. indicated a slight benefit from adding phenobarbital to phototherapy in neonates with hemolytic disease of the fetus and newborn (HDFN). However, due to its slow action, phenobarbital is not the preferred treatment when effective phototherapy and exchange transfusions are available. There may be potential benefits to administering phenobarbital to mothers during pregnancy, as a retrospective study by Trevett et al. reported a reduced need for exchange transfusions, though these findings require further confirmation.

3]Metalloporphyrins:

Metalloporphyrins work by inhibiting heme-oxygenase, the enzyme responsible for converting heme into bilirubin, which reduces bilirubin production rather than enhancing its excretion. Treatment with metalloporphyrins may lower bilirubin levels in neonates and decrease the necessity for phototherapy and hospital stays. However, there is insufficient evidence to recommend the routine use of metalloporphyrins for treating hyperbilirubinemia.

4]Zink:

Oral zinc is believed to lower serum bilirubin levels by diminishing the enterohepatic circulation of bilirubin. However, recent systematic reviews by Mishra et al. and Sharma et al. found no evidence to support the use of zinc in treating neonatal hyperbilirubinemia. It appears to have no impact on the duration or incidence of phototherapy, nor on the age at which phototherapy begins.

5]Clofibrate:

Clofibrate stimulates glucuronosyl transferase, which converts bilirubin into a water-soluble form that can be excreted. It appears that clofibrate, when used alongside phototherapy, may reduce bilirubin levels and shorten the duration of phototherapy in term neonates. However, larger trials are necessary to assess its effectiveness more comprehensively. Further research is particularly important for cases of hyperbilirubinemia caused by hemolysis, as these neonates were excluded from some studies.

6]Prebiotic supplementation:

Recent research has begun to explore the potential benefits of periodic supplementation in treating neonatal hyperbilirubinemia. Prebiotics are believed to enhance gastrointestinal motility and stool frequency, reduce stool viscosity and enterohepatic circulation of bilirubin, and support the growth of beneficial gut bacteria while improving feeding tolerance. Preliminary results appear promising for both preterm and term neonates with hyperbilirubinemia, showing positive effects on total serum bilirubin levels and the duration of phototherapy.

7] Antenatal corticosteroid

Antenatal corticosteroid treatment has been demonstrated to enhance lung maturation in preterm infants and lower the risk of respiratory issues, particularly for those born before 34 weeks of gestation. While antenatal betamethasone given after 34 weeks does not seem to reduce the risk of respiratory disorders, recent studies indicate that it can decrease the likelihood of neonatal jaundice requiring phototherapy, potentially by promoting liver maturation. A randomized controlled trial comparing antenatal steroids to standard treatment is planned at our center in the near future.

REFERENCE

1. Myle AK, Al-Khattabi GH. Hemolytic disease of the newborn: a review of current trends and prospects.Pediatric health, medicine and therapeutics. 2021 Oct 7:491-498
2. De Winter DP, Hulzebos C, Van ‘t Oever RM, De Haas M, Verweij EJ, Lopriore E. History and current standard of postnatal management in hemolytic disease of the fetus and newborn. european journal of Pediatrics. 2023 Feb;182(2):489-500.
3. Kumar A, Patel MK, Chavda B, Ranjan A, Ahmad F. Hemolytic Disease of the Newborn: A study of 50 cases. International Journal of Scientific Study.2013;1(3):95-99.
4. Gerard J. Tortora,Bryan Derrickson Tortoras PRINCIPLE OF ANATOMY AND PHYSIOLOGY, Edition 15th
5. Dajak S, Ipavec N, Cuk M, Golubic Cepulic B, Mratinovic-Mikulandra J, Milardovic J, Stefanovic V. The outcome of hemolytic disease of the fetus and newborn caused by anti-Rh17 antibody: analysis of three cases and review of the literature.Transfusion medicine and hemotherapy. 2020 Oct 3;47(3):264-271.
6. Drabik-Clary K, Reddy VV, Benjamin WH, Boctor FN. Severe hemolytic disease of the newborn in a group B African-American infant delivered by a group O mother. Annals of Clinical & Laboratory Science.2006 Mar 20;36(2):205-207.
7. C. Edwin Kinley.ERYTHROBLASTOSIS FETALIS.DALHOUSIE MEDICAL JOURNAL.
8. Kagan A., Hemolytic disease of the newborn (erythroblastosis fetalis) (Doctoral dissertation, Boston University).
9. Kennedy MS. Hemolytic disease of the fetus and newborn (HDFN), Modern Blood Banking & Transfusion Practices. 6th ed. New Delhi: Jaypee. 2013:427-438.
10. Avinash Patil,Brian Brocato, Rebecca A. Uhlmann, and Giancarlo Mari, Erythroblastosis fetalis. CLINICAL MATERNAL–FETAL MEDICINE ONLINE, 2nd edition.
11. De Haas M, Thurik FF, Koelewijn JM, van der Schoot CE, Haemolytic disease of the fetus and newborn, Vox sanguinis. 2015 Aug; 109(2):99-113.

12. Dubey R, Trigunait P, Pawar A, Yadav A. Haemolytic disease of the fetus and newborn: past, present and future considerations.In ASMS 2019.
13. Ifeanyi OE, International Journal of Pharmacotherapy.
14. Esan AJ. Hemolytic disorders of the newborn, current methods of diagnosis and treatment: a review study, J Hematol Blood Transfus Disord. 2016: 3(008).
15. Lofft TFm, Diagnosis of Erythroblastosis Fetalis, University of Western Ontario Medical Journal. 1959 1;29(3):82-84.
16. Anil Narang and Navecn Jain, HAEMOLYTIC DISEASE OF NEWBORN. Sahel Medical Journal, Vol. 4, No.4, October - December 2001 (174 - 180).
17. Das S. Hemolytic Disease of the Fetus, Blood Groups. 2019:10:25.
18. Ree IM, Smits-Wintjens VE, van der Bom JG, van Klink JM, Oepkes D, Lopriore E. Neonatal management and outcome in alloimmune hemolytic disease. Expert review of hematology, 2017 Jul 3;10(7):607-616.
19. Ross MB, de Alarcon P. Hemolytic disease of the fetus and newborn. NeoReviews. 2013 Feb 1;14(2): e83-88.
20. Sainio S, Nupponen I, Kuosmanen M, Aitokallio-Tallberg A, Ekholm E, Halmesmäki E, Orden MR, Palo P, Raudaskoski T, Tekay A, Tuimala J. Diagnosis and treatment of severe hemolytic disease of the fetus and newborn: a 10-year nationwide retrospective study. Acta Obstetricia et Gynecologica Scandinavica. 2015 Apr;94(4):383-390

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