Review Article

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An overview of recent advances in the prevention of erythroblastosis fetalis

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Abstract:

Erythroblastosis fetalis is one of the leading causes of death among newborns and fetuses in India. This condition is characterized by maternal immunoglobin G antibodies destroying the red blood cells (RBCs) of the neonate or fetus, resulting in potentially life-threatening consequences. When a mother with an Rh-positive blood group has a fetus with an Rh-negative blood group, the fetal RBCs trigger maternal antibodies against Rh-antigens. Anti-D antibodies are activated as a result of this process, which is known as isoimmunization. As a result of the antibody reaction, all of the erythrocytes are destroyed, resulting in hemolysis, bilirubin release, and anemia. Intravascular transfusions and intraperitoneal transfusions are examples of antenatal therapies that potentially avoid dangers to the fetus in the early stages of pregnancy. Phototherapy, exchange top-up transfusions, and intravenous immunoglobulin (IVIG) injections are examples of postnatal therapies (IVIG). IVIG therapy is highly recommended since it has a low risk of adverse medication responses and a wide range of survival rates. To avoid isoimmunization, anti-Rh D therapies are indicated. Noninvasive identification of the fetal human platelet antigen 1 genotype using cell-free fetal DNA obtained from maternal blood is one example of progress. This is still in the early stages of research as preventive medicine, the platelet equivalent of Rho (D) Immune Globulin Human (RhoGAM). The erythroblastosis fetalis is highly preventable when it is diagnosed at its early stages. Regular screening of all the patients with ABO incompatibility is necessary to prevent the risks of erythroblastosis fetalis.

Keywords:

Antenatal treatment, current preventive measures, erythroblastosis fetalis, hemolytic disease of the newborn and fetus, postnatal treatment

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Introduction

In India, the estimated risk of erythroblastosis fetalis in newborns or fetuses is about 2.9%, implying that 2196 babies are at risk and require intervention every day. Erythroblastosis fetalis, also known as hemolytic disease of the newborn and fetus (HDFN), is a common immune-mediated hematological disorder characterized by the destruction of the neonate's red blood cells (RBCs) or the fetus by maternal immunoglobin G antibodies, which can result in potentially fatal complications.[1,2] The Rhesus factor is the surface antigen of the erythrocytes. This Rh blood group consists of multiple antigens over 50, in that antigen D is responsible for the Rh hemolytic disease due to its immunogenicity. The presence of the D antigen determines the person's Rh positive or Rh negative on the surface of the RBCs. This hemolytic disease is highly preventable but may become fatal if left untreated.[3]

Rh-blood grouping system

The Rh blood grouping system categorizes RBCs based on the presence or lack of the Rh antigen on their cell membranes. They are commonly known as the Rh factor. There are several other Rh antigens, but the first and most frequent one is the Rh D, which generates the most severe immunological response and is the main predictor of the Rh characteristic.[4]

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Etiology and Pathophysiology

Rh–hemolytic disease is caused due to the incompatibility occurring between the blood of the fetus and the mother. When the blood of the fetus tends to cross the incompatible RBCs of the mother, the mother's immune system would consider that as an antigen and begins to attack by producing antibodies. During pregnancy or birth, this crossover usually occurs through the placenta. The mother's immune system develops memory and results in severe complications to the fetus in successive pregnancies, where the antigens would be again exposed.[5] In detail, the mother carrying an Rh-positive blood group carrying a fetus with Rh-negative blood group, the fetal RBC cells stimulate the maternal antibodies against the Rh antigens.[6] This process results in the activation of anti-D antibodies through a process known as isoimmunization. In return, this antibody response destroys all the erythrocytes, leading to the formation of hemolysis, subsequently the release of bilirubin and anemia.[7] The entire pathophysiology is summarized in the flowchart [Figure 1]. Complications of erythroblastosis fetalis include hepatomegaly, hypoproteinemia, portal hypertension, ascites, edema, polyhydramnios, and pericardial effusion.

Clinical Manifestations

- Hydrops fetalis: This is a condition in which fluid builds up in the fetus's body, causing ascites, pleural effusion, pericardial effusion, skin edema, and other symptoms.[7] Pericardial effusion can obstruct breathing and lead to congestive heart failure[8]
- Congenital anemia: Destruction of the RBCs may accumulate bilirubin in the fetus's body, causing hyperbilirubinemia and jaundice. This high level of bilirubin is severely fatal as it reaches the brain, causing kernicterus, which leads to neurological abnormalities such as speech/hearing difficulties and cerebral palsy.[9]

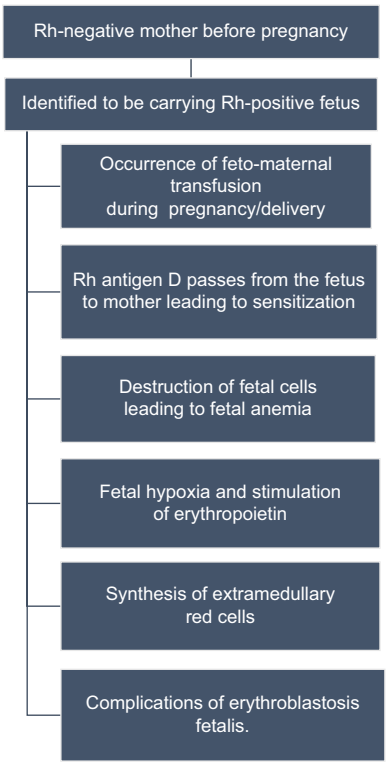

Figure 1: Pathophysiology of erythroblastosis fetalis

Differential Diagnosis

- Johnson *et al*. stated in their pilot study that severe glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency could be the cause of acute hemolysis leading to kernicterus in patients[10]
- Isoimmunization, alpha-thalassemias, RBC membrane abnormalities, for example, hereditary spherocytosis, elliptocytosis, and hemangiomas (Kasabach–Merritt syndrome)
- Acquired conditions, such as sepsis and infections containing TORCH (toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV).

Management of Erythroblastosis Fetalis

Antenatal treatment:

In severe cases, intrauterine transfusions (IUTs) are necessary to treat fetal anemia so that it can reduce the chances of hydrops fetalis in infants.[11] Studies have shown success and survival rates for hemolytic disease during the early days of pregnancy.[12] Two techniques are used to treat fetal anemia using IUTs, including intraperitoneal transfusions and intravascular transfusions.

1. Intraperitoneal transfusions: This procedure involves utilizing ultrasonography to guide a needle through the mother's abdomen and uterus into the fetus's abdominal cavity. The RBCs are taken into circulation through the subdiaphragmatic lymphatics after being injected into the baby's abdominal cavity. Rh-negative packed red cells with a hematocrit of 80% that have been crossmatched with the mother are routinely transfused[13]
2. Intravascular transfusions: This is a widely used method to treat fetal anemia and prevent hydrops fetalis in infants. This procedure involves transfusing Rh-negative blood group type O having a hematocrit of 80% that has been crossmatched with the mother to the fetal umbilical vein.[14]

Postnatal Treatment

1. Phototherapy: The most severe and prominent clinical manifestation of this disease is bilirubin-induced

neurologic dysfunction which leads to chronic kernicterus and encephalopathy. The standard treatment regimen for severe hyperbilirubinemia is phototherapy, and if required, exchange transfusions are done.[15] A study conducted by De Boer *et al*. concluded that infants treated with IUT require a lesser period of phototherapy than other infants suffering from HDFN.[16] The period of phototherapy must be considered according to the gestational age, severity, and the cause of the hyperbilirubinemia

2. Exchange and top-up transfusions: Exchange transfusions are a life-saving treatment option in treating neonatal jaundice in hemolytic disease of the newborn. This procedure eliminates neonatal anemia and reduces the risk of congestive heart failure. Studies have demonstrated the importance of exchange transfusion in the treatment of and prevention of kernicterus.[17] In this procedure, the fetus is replaced with fresh blood and plasma components. The use of exchange transfusion is indicated by a cord bilirubin level >4.5 mg/dL or a cord hemoglobin level <11 g/dL[18,19]
3. Intravenous immunoglobulins (IVIGs): Apart from the other treatment options available for HDFN, the recent administration of IVIGs has potentially been shown to reduce the risks of neonatal jaundice. It is considered to be a prophylaxis treatment for the prevention of HDFN and reduce the chances of kernicterus or isoimmune hemolytic jaundice in patients. A study conducted by Mayer *et al*. to determine the efficacy of IVIG concluded that early initiation of immunoglobulin therapy (1 g/1 kg/week) could improve the outcomes of risk in the fetus.[20] R. Gottstein and Cooke conducted a systematic review of the IVIG use in hemolytic disease of the newborn and concluded that the use of IVIG is essential to prevent the complications of HDFN and also it is an effective treatment. The use of IVIG and phototherapy significantly reduces the patient's hospital stay.[21] The American Academy of Pediatrics supports IVIG as an additional treatment in the management of HDFN, with repeat dosage if necessary.[22] IVIG is highly recommended since it possesses very few adverse drug reactions and has a huge range of survival rates
4. According to the recommendation of the American Association of Blood Banks, continuous screening before the administration of Rh-D immunoprophylaxis at 28 weeks of the gestation period, fetomaternal hemorrhage, and postpartum events is essential to reduce the risks of the infant[23]
5. Anti-RhD is usually given in 300 mcg doses in the second and third trimesters and postpartum if needed. The suggested amount during the first trimester is 150 mcg. When 15 mL or fewer fetal RBCs (or 30 mL of whole blood) reach the maternal circulation, a one-time treatment of 300 mcg anti-RhD should prevent isoimmunization. A rosette test is a qualitative method of determining whether or not someone has Fetomaternal Hemorrhage (FMH). If the rosette test is positive, the Kleihauer–Betke test should be used to establish the quantity of fetomaternal blood mixing and if additional doses of Rh-D immunoprophylaxis are required[24]
6. Another advancement is the noninvasive determination of the fetal human platelet antigen 1 genotype using cell-free fetal DNA acquired from maternal blood. The development of a prophylactic product that is the platelet equivalent of RhoGAM is currently in its early phases of development (RhoGAM).[25] These treatment measures can be widely used to prevent the severe complications of HFDN and even the death of the fetus.

Recent Advancements in Preventing Erythroblastosis Fetalis

Emerging advancements are evolving around the use of IVIG over decades. Despite the lack of evidence, IVIG may be beneficial in other forms of Rh hemolytic disorders, such as anti-C and anti-E. It might also be used to treat nonimmune hemolytic anemia, such as G6PD deficiency. Immune thrombocytopenia and sepsis are two more indications of IVIG in newborns. More evidence and research are required to gather more information regarding the future use of IVIG in fetuses and newborns. In addition, hemolytic disease by ABO incompatibility has also emerged as a serious problem; regular screening is necessary to detect the presence of Rh-negative antibodies to eliminate the risks to the fetus. The HDFN can be prevented if treated promptly; the cause for the complications should be identified earlier to reduce or eliminate the risks to the fetus or infant.

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Conflicts of interest

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