HEMOLYTIC DISEASES OF NEWBORN: A REVIEW

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ABSTRACT
Haemolytic Disease of the New born (HDN), also known as erythroblastosis fetalis, isoimmunization, or blood group incompatibility, occurs when foetal red blood cells (RBCs), which possess an antigen that the mother lacks, cross the placenta into the maternal circulation, where they stimulate antibody production. The antibodies return to the foetal circulation and result in RBC destruction. It is great threat to the newly born babies. As our future is in the hands of new generation we have to keep them safe. So, the management and awareness about the haemolytic disease is also an important measure to be taken. so here we can see the detailed description about the management, treatment, diagnosis, and prevention of the haemolytic disease of the new born.

KEYWORDS: Haemolytic disease, new-born, antigen, antibody, rhesus incompatibility, jaundice, RhoGAM.

INTRODUCTION
The term haemolytic disease of new born (HDN) is known as erythroblastosis fetalis isoimmunization. “Haemolytic” means breaking down of RBC. “Erythroblastosis” refers to the making of immature red blood cells. ‘Fetalis’ refers to foetus. Normally, red blood cells last for about 120 days in the body. In this disorder, red blood cells in the blood are destroyed earlier than normal. The antibodies responsible for haemolysis can be naturally occurring or can develop as a result of a sensitising event such as pregnancy or transfusion. The most well recognised is rhesus alloimmunisation. It occurs when the mother is RH negative and father is Rh negative. If the foetus possess an antigen from father that the mother lacks, and thus the babies red blood cells cross the maternal circulation and thus stimulating antibody production in the mother’s body. These antibodies will return to the foetal circulation and will cause RBC destruction. This sequence of events occurs normally during delivery when the placenta
detaches. But it can happen anytime when the blood cells of the two circulation mixes like in abortion or miscarriage with a fall or during an invasive prenatal testing procedure. This occurs as the mother’s immune system will identify the baby’s Rh-positive blood cells as a foreign body, thus producing corresponding antibody to destroy these foreign cells. It is not much severe in case of first pregnancy than in second and further pregnancies. The mother’s immune system will keep the antibodies even in a future pregnancy. There are rarely any problems during primary exposure but subsequent pregnancies result in large amounts of maternal anti-D antibodies being produced and the risk increases with each gestation. As the antibodies destroy the red blood cells, the baby can become sick. This is called erythroblastosis fetalis during pregnancy. In the new born, the condition is called haemolytic disease of the new born. When the mother’s antibodies attack the red blood cells, they are broken down and destroyed. This makes the baby anaemic. It is actually a blood group incompatibility due to Rh(D) incompatibility.\[^{[24][25]}\]

**SIGNS AND SYMPTOMS**

Hemolytic anemia - Untreated profound anemia can cause high-output heart failure, with pallor, enlarged liver and/or spleen, generalized swelling, and respiratory distress. HDN can be the cause of hydrops fetalis, an often-severe form of prenatal heart failure that causes fetal edema.

Jaundice – hemolysis leads to elevated bilirubin level. After delivery bilirubin is no longer cleared from the neonate’s blood via placenta and thus there arises a symptom of jaundice arises within in 24 hours of birth which include the yellowish coloration of skin and eyes. There will a possibility for acute as well as chronic kernicterus due to the rapid destruction of blood cells. It is important to note that isoimmunization is a risk factor for neurotoxicity and lowers the level at which kernicterus can occur.\[^{[23]}\]
Figure 2: This infant is presented with jaundice 8 week after birth. The cause was hemolytic disease of the newborn due to Rh incompatibility. The mother’s fingers were shown for contrast.

PATHOPHYSIOLOGY

Figure 3: Diagrammatic representation of pathophysiology of HDN.
The antibodies responsible for hemolysis can be naturally occurring or can develop as a result of a sensitizing event such as pregnancy or transfusion. The most well recognized is rhesus alloimmunization which begins with red blood cells from a rhesus-positive fetus crossing the placental barrier during pregnancy and delivery, and entering the maternal blood circulation. A rhesus-positive father and a rhesus-negative mother are required for this situation to develop. The incompatible antigens introduced result in a primary immune response and stimulate the production of maternal antibodies. A very small amount of fetal maternal hemorrhage (FMH) needs to occur (less than 0.1 ml) and most go unrecognized. Primary exposure can also be the result of amniocentesis, chorionic villus sampling and cordocentesis.

There are rarely any problems during primary exposure but subsequent pregnancies result in large amounts of maternal anti-D antibodies being produced and the risk increases with each gestation. These are capable of crossing the placenta, where they affix to fetal red blood cells, which then become recognized as 'foreign' by the fetal immune system and hemolyzed by fetal macrophages and lymphocytes. If the rate of red cell destruction exceeds the rate of production it results in fetal anemia which, if severe, can lead to fetal heart failure, fluid retention and swelling (hydrops). Red cell breakdown results in bilirubin release which is not a problem during fetal life as it is cleared by the placenta. After birth, however, the immature neonatal liver is not capable of handling a high bilirubin load and this can result in severe neonatal jaundice. High levels of jaundice if untreated can result in permanent brain damage (kernicterus) because of deposition of bilirubin in certain areas of the neonatal brain.

**DIAGNOSIS**

**Testing**

Testing for HDN involves blood work from both mother and father, and may also include assessment with amniocentesis and Middle Cerebral Artery scans.

**Mother**

Blood testing for the mother is called an Indirect Coombs Test (ICT) or an Indirect Agglutination Test (IAT). This test tells whether there are antibodies in the maternal plasma. It is also known as antibody testing. Antibody tests are done to find certain antibodies that attack red blood cells. Antibodies are proteins made by the immune system. It is of two types, direct and indirect coombs test. Haemolytic disease of new-born gives indirect coombs test. It is used to detect the antibodies or compliment protein that are bound to the surface of red blood cells. It is done by taking the blood sample and the red blood cells are washed to
remove the patient’s own plasma. Then it is incubated with coombs reagent which is an anti-human globulin. The positive test shown an agglutination of red blood cells with a visual indication that antibodies are bound to surface of blood cells

**Father**

Blood is generally drawn from the father to help determine foetal antigen status. If he is homozygous for the antigen, there is a 100% chance of all offspring in the pairing to be positive for the antigen and at risk for HDN. If he is heterozygous, there is a 50% chance of offspring to be positive for the antigen. This test can help with knowledge for the current baby, as well as aid in the decision about future pregnancies.

**Foetus**

There are several possible ways to test the foetal antigen status.

1. **Free Cell DNA**
2. **Amniocentesis**
3. **Doppler ultra-sonographic method**
4. **Chorionic Villus Sampling**
5. **Middle cerebral artery scans**

Of the three, antigen status has been determined, and assessment may be done with MCA scans.

1. **Free cell DNA:** Blood is taken from the mother, and using PCR, can detect the K, C, c, D, and E alleles of foetal DNA. This blood test is non-invasive to the foetus and is an easy way of checking antigen status and risk of HDN.

2. **Amniocentesis:** The standard test to predict whether the fetus needs a blood transfusion is examination of the amniotic fluid. To obtain this fluid a needle has to be inserted in the womb, which has a risk of preterm delivery, infection and making the disease worse. This is called amniocentesis. Amniotic fluid contains viable fetal cells which can be grown in tissue-culture medium and used for chromosome analysis, enzyme assay, and DNA analysis for single-gene disorders.

3. **Doppler ultra-sonographic method:** A Doppler ultrasound is a non-invasive test that can be used to estimate the blood flow through your blood vessels by bouncing high-frequency sound waves (ultrasound) off circulating red blood cells. It changes sound
waves into an image that can be viewed on a monitor. Doppler ultrasonography can detect the direction, velocity, and turbulence of blood flow. It is frequently used to detect problems with heart valves or to measure blood flow through the arteries. Thus, the extend of haemolysis can be detected by this method.

4. **CVS (chorionic villus sampling):** It is possible as well to test foetal antigen status but is not recommended. CVS is no longer used due to risk of worsening the maternal antibody response. Chorionic villus is a placental tissue which can be collected by using a catheter.

5. **Middle cerebral artery:** Peak systolic velocity is changing the way sensitized pregnancies are managed. This test is done noninvasively with ultrasound. By measuring the peak velocity of blood flow in the middle cerebral artery, a MoM (multiple of the median) score can be calculated. MoM of 1.5 or greater indicates severe anaemia and should be treated with IUT.

**TREATMENT**

After birth, treatment depends on the severity of the condition, but could include temperature stabilization and monitoring, phototherapy, transfusion with compatible packed red blood, exchange transfusion with a blood type compatible with both the infant and the mother, sodium bicarbonate for correction of acidosis and/or assisted ventilation.

- **Platelet transfusion**- Platelet transfusion: transfer of blood platelets from a donor to a recipient or reinfusion to the donor

- **Exchange transfusion**- Exchange transfusion is used when bilirubin reaches either the high or medium risk lines on the nomogram provided by the American Academy of Pediatrics. Cord bilirubin >4 is also indicative of the need for exchange transfusion.

- **Plasma Exchange**- It is widely used treatment of immune-mediated disease. This treatment is applied to the pregnant women with high antibody titer, or that has past history of stillbirth due to HDN. This procedure is effective in decreasing the antibody titer and quantity of antibody. Plasma exchange can reduce antibody titer up to 75%. Besides that, it also uses for a way to delay the need for fetal intervention that has been hydrops fetalis (edema) in which before 22-week gestation in a previous pregnancy

- **Intravenous Immune Globulin**- Intravenous immune globulin (IVIG) is made up from plasma isolated. This treatment strengthens body immune system beside to treat immune deficiency. Intravenous Immunoglobulins were found to decrease hemolysis leading to
reduction in serum bilirubin level The normally given Rh immunoglobulin is normally called as RhoGAM.

- **Phototherapy** - Phototherapy for ABO hemolytic disease of the newborn infant usually reduces or prevents a further rise in serum bilirubin levels. In light-treated infants, peak bilirubin concentrations do not occur after the third day of life and exceed 20 mg. per cent in only 10 per cent of the infants. Phototherapy is not indicated for infants with ABO disease of mild onset and severity. In severely affected infants, a trial period of phototherapy is justified but must not exclude consideration of exchange transfusion for control of rapidly rising serum bilirubin levels.

- **Intrauterine Transfusion (IUT)** - Red Blood Cells (RBCs) are infused into abdominal cavity of fetus and then absorbed into fetal circulation to avoid hydrops fetalis and fetal death. Can be done as early as 17 weeks. In intraperitoneal IUT, a needle is passed through the mother’s abdomen and into the abdomen of the fetus by the help of ultrasound image to determine the position of the fetus and placenta.

**COMPLICATIONS**

Mild anemia, hyperbilirubinemia and jaundice. The placenta helps rid some of the bilirubin, but not all. Thus, arises the condition of jaundice. Mild anemia is due to the destruction of red blood cells.

Severe anemia with enlargement of the liver and spleen. When these organs and the bone marrow cannot compensate for the fast destruction of red blood cells, severe anemia results and other organs are affected.

Hydrops fetalis is another condition that occurs as the baby's organs are unable to handle the anemia. Hydrops fetalis is an excess accumulation of fluid in the fetus. Depending on the severity and cause of hydrops, there may be edema of fetus and placenta, ascites, pleural effusions and/or pericardial effusion. The heart begins to fail and large amounts of fluid buildup in the baby's tissues and organs.

Kernicterus is the most severe form of hyperbilirubinemia and results from the buildup of bilirubin in the brain. This can cause seizures, brain damage, deafness, and death.
Other complications that arises due to hemolytic newborn disease are as follows:

- Bilirubin Induced Neurological Dysfunction
- Cerebral Palsy
- Kernicterus
- Neutropenia
- Thrombocytopenia
- Discoloration of teeth
- Infection and metabolic disorders
- Schizophrenia

**CONCLUSION**

Haemolytic Disease of the New born (HDN), also known as erythroblastosis fetalis, isoimmunization, or blood group incompatibility, occurs when foetal red blood cells (RBCs), which possess an antigen that the mother lacks, cross the placenta into the maternal circulation, where they stimulate antibody production. The antibodies return to the foetal circulation and result in RBC destruction. There is a great chance of risk to the new-born due to this. So, we have to be aware of the possible preventions, managements and the diagnosis of this haemolytic diseases of new-born. As prevention is better than cure we have to prevent this threat before it happens than treating it. As todays newborn are tomorrows future it is our responsibility to keep them safe.

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