Blood Type Incompatibility and Haemolytic Disease of the Newborn

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Overview

Haemolytic disease of the newborn is a blood disorder that causes baby's red blood cells to break down quickly, known as haemolysis. Haemolysis causes anaemia and jaundice during the first few days to weeks of baby's life.[1]

Haemolytic disease can occur when there is a mismatch between the mother's and baby's blood type and/or Rh factor during pregnancy.

Terminology

HDN: Haemolytic disease of the newborn

HDFN: Haemolytic disease of the fetus and newborn

RBC: Red blood cells

Haemolysis: Breaking down of Red Blood Cells

Antigen: Any substance that prompts the body to trigger an immune response against it.

Antibody: Produced when the body detects an antigen

Blood typing

The ABO system: 4 main blood groups

Blood group	Antigens on RBCs	Antibodies in plasma
A	A antigens	Anti B antibodies
B	B antigens	Anti A antibodies
O	No antigens	Both Anti A and Anti B antibodies
AB	Both A and B antigens	No antibodies

The Rh system and other minor blood group system

The Rh (Rhesus) factor is an antigen that can be found on the surface of RBCs.

Rh blood type is **positive** when the Rh protein is present or **negative** when the Rh protein is absent.

The Rh factors are: D or d, C or c, E or e

Other blood group antigens can be responsible for causing HDN, for example anti-c, -K, -E, -Fya. These antibodies occur in about 0.5% of pregnancies and may occasionally cause severe haemolysis.[2]

Maternal antibodies cross the placenta

During pregnancy, some of the mother's antibodies are transported across the placenta and enter the fetal circulation. This is necessary because by the time of birth, newborns have only a primitive immune system, and the continuing presence of maternal antibodies helps to ensure that they survive while their immune system matures. A downside to this protection is that by targeting fetal RBCs, maternal antibodies can cause HDN.[1]

Rh incompatibility (most commonly D antigen)

Rh incompatibility occurs when a mother who is Rh negative (who has circulating anti Rh antibodies from a previous exposure to Rh positive antigens either through blood transfusion or during prior pregnancy and delivery) gives birth to a newborn who is Rh positive. During pregnancy, those antibodies will cross the placenta and vigorously attack the baby's Rh positive RBC by adhering to and then lysing the cells. First pregnancies are not generally at risk for Rh incompatibility except in those instances where a mother was stimulated to produce anti Rh through a blood transfusion.

Rh sensitisation occurs during the first pregnancy

Sensitisation to an antigen occurs when the immune system encounters an antigen for the first time and mounts an immune response.

In Rh incompatibility, a Rh negative mother may first encounter the Rh antigen while being pregnant with Rh positive baby or by receiving a blood transfusion of Rh positive blood. Once a mother has been sensitized to Rh D antigen, Anti D is produced.

Only a small amount of fetal blood needs to enter the mother's circulation for sensitisation. Typically, this sensitisation occurs during the delivery of the first child (fetal maternal haemorrhage is common during labour). It may also occur during medical procedures such as termination of pregnancy or chorionic villus sampling. Sensitisation can also occur earlier in the pregnancy for example during a prenatal bleed or miscarriage.[3]

HDN occurs in subsequent pregnancies

In subsequent pregnancies, a repeat encounter with Rh D antigen stimulates the rapid production of type IgG anti D, which can be transported across the placenta and enter the fetal circulation. Once in the fetal circulation, anti D attaches to the Rh D antigens found on the fetal RBCs, marking them to be destroyed.[4]

Severe cases of HDN can be caused by anti-D, anti-C and anti-K.

ABO incompatibility

ABO incompatibility occurs by the same general mechanism as Rh incompatibility. Risk factors for ABO incompatibility are present in 12–15% of pregnancies, but evidence of fetal Sensitisation (positive direct Coombs test) occurs in only 3–4%.[5]

Women with Type O blood are most commonly impacted, since they carry both anti-A and anti-B antibodies. In type O blood, the antibody is predominantly 7S-IgG and is capable of crossing the placental membrane. Because of its larger size, the mostly 19S-IgM antibody found in type A or Type B blood cannot cross this placental membrane[5]. Hence, in group O individuals, IgG anti-A and anti-B will cross the placenta and cause haemolysis of fetal RBCs. If a woman has high level of IgG anti-A or anti-B, this may affect her baby and produce increased jaundice.[2]

HDN due to ABO incompatibility is usually less severe than Rh incompatibility because of the following reasons:

- Fetal RBCs express less of the ABO blood group antigens compared with adult levels.
- In contrast to the Rh antigens, the ABO blood group antigens are expressed by a variety of fetal tissues, reducing the chance of anti A and anti B binding their target antigens on the fetal RBCs.
- The half-life of the placenta passing Rh antibody molecule is approximately 30 days. On the other hand, incompatible alpha and beta antibodies are quickly neutralized and eliminated from the body of newborns.[4]

Although very uncommon, cases of ABO HDN have been reported in infants born to mothers with blood group A and B.[6]

Diagnosing HDN

Direct Antiglobulin Test (DAT)

The DAT detects maternal antibodies in the in the **newborn serum** that have already bound to fetal RBCs.[4]

Indirect Antiglobulin Test (IAT)

This test finds antibodies in the **maternal serum**. By finding maternal antibodies before fetal RBCs have been attacked, treatment can be given to prevent or limit the severity of HDN.

The direct antiglobulin test (DAT) and indirect antiglobulin test (IAT) are sometimes referred to as the direct and indirect **Coombs** test, as they are based on tests developed by Coombs, Mourant and Race in 1945.

Jaundice and other complications of HDN

Jaundice caused by haemolysis usually occurs within the first 48 hours after birth. [7]

The rate of haemolysis depends on the titre of maternal antibody and hence the nature of HDN can be mild, moderate, or severe. The haemolysis of the RBCs produces bilirubin. When bilirubin levels are high, the neonate's immature liver is unable to metabolise the increased amount of bilirubin and it causes jaundice. This shows as a yellow discolouration of the skin and the whites of the eyes.

In cases where there is a greater increase in the rate of haemolysis and the bilirubin level continues to rise, it may enter the brain to cause bilirubin encephalopathy, a potentially fatal condition that leaves permanent neurological damage in the babies that survive.

An even greater rapid and prolonged destruction of the RBCs leads to severe anaemia in the fetus. The liver, spleen and other organs increase their production of RBCs to compensate for their loss. The drive to produce RBCs causes the liver and spleen to increase in size (hepatosplenomegaly) and liver dysfunction can occur. Immature RBCs (erythroblasts) spill into the circulation, giving rise to the alternative name of this disease, erythroblastosis fetalis. A complication of severe HDN is hydrops fetalis, in which the fetal tissues become swollen. This condition is usually fatal, either in utero or soon after birth.[4]

On the other hand, physiological jaundice is a very common phenomenon in the newborn, occurring in more than 60% of term babies. It usually appears at about 72hrs, peaks at 4 days and declines over the next week. If the baby is alert, has good muscle tone, is feeding well, passing urine normally and is content between feeds, no action required other than to patiently wait for the jaundice to dissipate.[8]

Assessment of Jaundice

Measurement of jaundice can be done either by blood sample or transcutaneous means.

Serum bilirubin (SBR) is a laboratory test and is the gold standard for measuring levels of jaundice. Capillary blood gas samples (CAP) analysed by the blood gas analyser can also be used for measuring bilirubin and is an acceptable alternative. This is a smaller sample and less likely to become haemolysed.

Jaundice levels can also be measured transcutaneously (in the skin) using a transcutaneous bilirubinometer (TcB). Transcutaneous bilirubin measurements are useful in certain settings as are instant and can help avoid delays in treatment. They can also indicate the need for formal SBR testing. TcB measuring can therefore be used as screening tool for jaundice in certain infants in certain circumstances. It does not replace the SBR but helps to determine more accurately than visual assessment if an SBR/CAP specimen required.[9,10]

Prevention of HDN

Rh D immunoglobulin

Rh D immunoglobulin is the most common treatment to prevent antibody production in people who are Rh negative. The Rh D immunoglobulin neutralises any Rh D positive antigens that may have entered the mother's blood during pregnancy and hence, will significantly decrease the risk of next baby having rhesus disease.

The use of Rh D immunoglobulin prophylaxis in pregnancy is described in a regional health pathway. [11] Usually, women who are Rh D negative receive an injection of Anti D at around 28 weeks of gestation, which is the time when fetal RBCs start to express the D antigen. The second prophylactic dose is at about 34 weeks gestation, a few weeks before labour during which feto-maternal haemorrhage is high. A final dose of Anti D is given within 72 hours after baby is born[4]. Half-life of passive anti D from Rh D immunoglobulin is approximately 3 weeks. Rh D immunoglobulin won't help if mother's body has already produced antibodies.

Kleihauer testing gives an indication of the number of fetal cells in the maternal blood. This test can be used for determining the amount of fetal maternal haemorrhage determining the Rh D immunoglobulin requirement. A negative Kleihauer test does not mean Rh D immunoglobulin is not needed as the test will not detect traces of fetal cells.[2]

Maternal **Rh D immunoglobulin (anti D) administration** during pregnancy **does not cause neonatal haemolysis**.

Numerous studies have suggested that while small amounts of passive anti D may cross the placenta, the antenatal administration of anti D immunoglobulin does not have adverse consequences for the fetus.[12]

Intrauterine transfusion

A blood transfusion is given to the fetus to replace RBCs that are being destroyed by the Rh sensitized mother's immune system. The goal of intrauterine transfusion is to prevent (or treat) fetal hydrops until a safer gestational age is reached. This transfusion can be given though the fetal abdomen (intraperitoneal) or more commonly into the umbilical vein or artery.[13]

Treatment of HDN

Phototherapy

Phototherapy is a treatment for jaundice. Phototherapy uses specific types of light which converts unconjugated bilirubin molecules into water soluble isomers that can be excreted by the usual pathways. Blue light is most effective for phototherapy as it penetrates the skin and is absorbed by the bilirubin to have the photochemical effect.

Refer to Neonatal Clinical Resource for more information about phototherapy chart and using different phototherapy equipment.[12]

Exchange blood transfusion

An exchange blood transfusion is carried out in haemolytic disease to avoid the dangers of Bilirubin encephalopathy, by removing blood containing maternal antibodies and bilirubin from the baby's circulation and replacing it with fresh Rh negative blood, the ABO group being compatible with the baby's.[13,14]

IV immunoglobulin

When the jaundice is caused by the rhesus disease, neonatal intravenous administration of immunoglobulin (IVIG) may be used. It is usually only used if phototherapy alone has not worked and the level of bilirubin in the blood continues to rise.

Intravenous immunoglobulin may reduce the need for a blood transfusion.[14]

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