Feto-maternal antigen incompatibility

Not Only Rh!

EWA BROJER
Institute of Hematology
and Transfusion Medicine, Warsaw
ebrojer@ihit.waw.pl
Prof. Ewa Brojer is a specialist at the laboratory of transfusion medicine.

BE&W

It sometimes happens that a mother's body reacts against certain particles present on the blood cells of the child she carries, with consequences that may be quite serious. Can such reactions be prevented?

Feto-maternal antigen incompatibility, which can lead to disease of the fetus, occurs when a pregnant woman produces antibodies to certain antigens her fetus inherited from its father, found on the surface of blood cells including erythrocytes, platelets or granulocytes. This can happen when the mother's body does not produce a certain antigen which is present in the fetus (the reverse never occurs). The effects may prove dramatic, as antibodies passed from the mother to the fetal blood destroy the cells of her own baby and may even lead to its death. A situation straight from an ancient tragedy: a healthy mother produces antibodies that damage her otherwise healthy child, and there is nothing she can do about it. Fortunately, as is often the case in biology, not every antigen incompatibility leads to antibody production in the mother's body. Likewise, not every "conflict" results in serious disease. If so, how often does it occur and are the consequences always serious? Can it be predicted and the consequences prevented? What treatment measures are available to protect the fetus? Before we answer these questions let us present certain historical facts, taking us back as far as the 17th century.

Ludwik Hirszfeld's underappreciated discovery

The first clinical descriptions of fetus/newborn hemolytic disease can be traced back to the 17th century. In 1609, Louise Bourgeois, a French midwife, assisted the birth of twins. One of them died immediately of generalized edema (hydrops fetalis), the other presented jaundice and neurological symptoms and died three days later. Many similar cases were also described. In 1925, the Polish scientist Ludwik Hirszfeld put forward the hypothesis of a possible correlation between the production of maternal antibodies and disease in newborns. This hypothesis was not accepted at first; the relation between disease and maternal antibodies and the cause of hemolytic disease of the fetus and newborn was further pursued in the 1930s and finally explained in 1940, with the discovery of the Rh antigen system by Karl Landsteiner and Alexander

S. Wiener, and the discovery of the RhD antigen by Philip Levine (1941).

Risk of 10%

Research material published in the 1940s reported that women who do not produce D antigen (Rh-negative blood group) may undergo alloimmunization induced by the RhD antigen present in the fetus. This process normally occurs during labor, when fetal cells infiltrate into the maternal circulatory system. This explains why the Rh conflict and disease of the fetus/newborn are observed in second pregnancies, when the mother produces anti D antibodies which cross the placenta. These antibodies bind to the RhD antigen on the surface of fetal erythrocytes. Such erythrocytes with antibodies are often described as "coated." This coating is a signal for the reticuloendothelial system to destroy these cells, which leads to anemia, in extreme cases resulting in the death of the fetus or newborn.

The incidence rate for hemolytic disease of the fetus/newborn due to RhD conflict used to be quite high (1/170 births). Fifteen percent of Caucasian women were at risk, since RhD-negative individuals represent 15% of the population. There is a 50% probability that the child of a RhD-positive father will not inherit the RhD antigen-coding gene and have RhD-negative blood type. In light of the above the "conflict" involving the D-antigen of the Rh system, as it is currently referred to, is assumed to affect approximately 10% of women.

In-depth knowledge of blood group characteristics is essential for safe and effective blood transfusion. Advancement in this field may save the lives of many children with hemolytic disease through exchange transfusion at birth or intrauterine transfusions. A turning point in the process of minimizing the incidence rate of fetal and newborn mortality due to RhD conflict came with the implementation of screening tests targeting RhD-negative women at risk of experiencing serological conflict.

Prevention of Rh-conflict

RhD-negative women are subject to regular antibody screening to determine if they produce anti-D antibodies and if so to determine their level. For various reasons the presence of antibody in their sera does not necessarily indicate fetal disease. The fetus may be RhD-negative and the antibodies may have been produced in a previous pregnancy, or for some reason maternal antibodies may not have crossed the placenta into the fetus. Women of the same blood group (ABO) as their child were more likely to produce anti-Rh antibodies. The issue of RhD conflict is still open to research and discussion and there seem to be several promising avenues to pursue.

Recently developed serological and DNA-based methods, as well as ultrasonogaphy, are being used for diagnostics of fetus/newborn disease due to alloimmunization. DNA methods help to determine whether the child inherited an antigen-encoding gene against which the mother's antibodies are directed. The procedure is safe and non-invasive, based on the analysis of fetal DNA in the sample of mother's plasma. In 2001 similar tests were also developed at the Institute of Hematology and Transfusion Medicine in Warsaw and have been in routine used ever since.

The real breakthrough in the field of RhD conflict research was brought about by the implementation of immunoprophylaxis. In 1966, two research groups from the UK and the USA demonstrated that antibody production in RhD-negative women is inhibited by administration of anti-RhD immunoglobulin immediately following labor. Immunoglobulin was found to capture and bind the RhD protein fragments that infiltrated into the mother's circulatory system during childbirth. As result the mother's

Useful information: At the beginning of pregnancy a pregnant woman should perform blood tests to determine blood group (ABO and RhD) and immune antibodies to red cell antigens. Serological conflict affects not only Rh-negative women (erythrocytes), but may also involve other blood cells (platelets and granulocytes). The Institute of Hematology and Transfusion Medicine in Warsaw specializes in performing diagnostic tests for detection of all such conflicts. Screening tests to determine the risk of conflict on platelets will be performed in 2014 and 2015, free of charge. For more information please visit www.konfliktplytkowy.ihit.waw.pl.

body is not stimulated by the fetal antigen to produce antibodies. Shortly after the phenomenon was observed the Polish Institute of Hematology (1973) started the production of anti-D immunoglobulin under supervision of Prof. Halina Seyfried and immunoprophylaxis of maternal-fetal conflict was introduced. A center for diagnosis of serological conflict was established andit closely cooperated with clinical centers for the treatment of fetuses and newborns throughout the country.

The program for prevention of RhD conflict, certainly one of the most spectacular medical achievements, is extremely effective; the incidence rate for RhD conflict has decreased from 1:170 to 1:1,000 births. The success is closely related to screening tests being introduced into routine practice. Nowadays, most pregnant women are aware of the necessity to determine their ABO and RhD blood group and screening for red blood cell antibody. RhD-negative women understand the need for post-partum immunoglobulin administration. It seems reasonable to ask, therefore, why cases of hemolytic disease are still being observed. This might be explained by negligence in immunoglobulin administration after childbirth, or by occasional uncontrolled leakage of fetal blood cells into the maternal circulatory system during pregnancy. In some countries anti-D immunoglobulin is administered as preventive measure not only after childbirth but already during pregnancy.

Although RhD conflict is well recognized, not many people are aware that serological conflicts also occur in RhD-positive women. It is therefore essential that appropriate tests be performed during pregnancy in all women, not only those who are RhD-negative.

"Conflicting" systems

Apart from antibody against D antigen, there are also antibodies directed against many other antigens on the surface of red blood cells responsible for destroying fetal/newborn red cells. The ABO and Rh systems are unquestionably the most widely recognized, but also other less known systems have been identified, including Kell, Kidd, and Duffy, all of which may be the cause for antibody production and hemolytic disease of the fetus/newborn. The incidence rate is the same as for the RhD conflict (1:1,000 births). Unfortunately, no immunoprophylaxis for these conflicts has as yet been developed, so such an infant's life can be saved only by early detection of antibodies in women, followed by appropriate diagnostic care, which includes antibody testing and ultrasound monitoring as well as transfusion.

All women regardless of blood type are at risk of serological conflict unrelated to the RhD system and therefore all pregnant women are subjected to regular antibody tests for detection of specific antibodies. It is noteworthy that such conflict may also involve blood cells other than erythrocytes (platelets and granulocytes included), when antibodies produced by the mother are responsible for thrombocytopenia or granulocytopenia in the child.

The risk of thrombocytopenia

Platelets are blood cells responsible for blood clotting. When the number of platelets is significantly below normal, thrombocytopenia is diagnosed, which may be responsible for petechiae and hemorrhages, including life threatening or even fatal bleeding into the central nervous system. Anti-platelet antibody production due to the incompatibility of feto-maternal antigens on platelets is observed in 1:1,500 births; in 10% of cases it is associated with hemorrhages into the central nervous system, which may sometimes be fatal. Negative effects of thrombocytopenia may also include microbleeding, which leads to various disabilities.

Cases of alloimmune thrombocytopenia have been diagnosed in Poland since the late 1970s. Research on the subject was performed at the Institute of Hematology and Transfusion Medicine by the team of Prof. Barbara Żupańska. A report on the first case of alloimmune thrombocytopenia in a Polish woman was published in 1985. The mechanism of the disease is similar to that observed in the RhD system. Most frequently the disease is caused by the anti-HPA-1a antibodies produced by the mother who does not carry the HPA-1a antigen (i.e. she is HPA-1a negative). Such women represent 2% of the population and can be identified by various diagnostic methods. The Institute of Hematology and Transfusion Medicine in Warsaw in cooperation with the University of Tromsø in Norway (the PREVFNAIT project) provides access to such tests to pregnant women (up to the 20th week

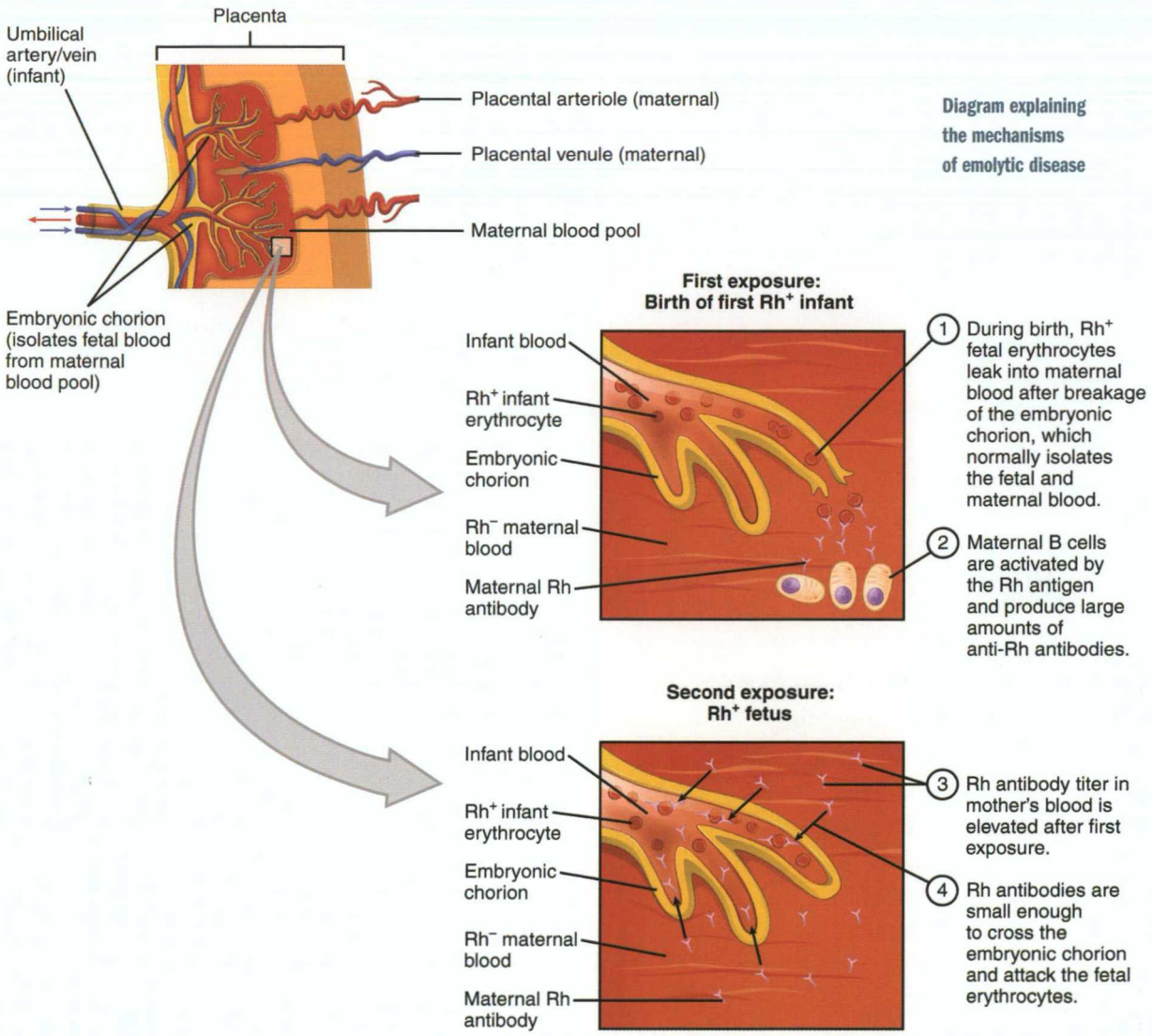

Diagram explaining the mechanisms of emolytic disease

of gestation). The aim is to further develop methods that will contribute to routine testing of pregnant women as well as to improve methods that help to determine the risk of fetal disease. The latter is particularly important for platelet conflicts, as such conditions are difficult to treat. One of our goals is to improve the methods of fetal antigen determination in DNA isolated from maternal blood as it is done for "red blood cell" incompatibility.

The last group of diseases caused by antibodies produced by pregnant women includes very rare serological conflicts (1/6,000 pregnancies) that involve granulocytes. Granulocytes are white blood cells responsible for fighting infections. Maternal anti-granulocyte antibodies destroy the baby's granulocytes, rendering it susceptible to often severe infections. Fortunately, the life-span of these antibodies is short and the disease is self-limited, though sometimes it may last up to six months. ■

Further reading:

Lankiewicz B., Żupańska B. (2003). Znaczenie przeciwciał innych niż anty-D w chorobie hemolitycznej płodu i noworodka [The importance of antibodies other than anti-D in hemolytic disease in the fetus and newborn]. *Gin. Pol., 74 (1)*: 48-54.

Dębska M. (2009) Alloimmunologiczna małopłytkowość płodu [Autoimmunological thrombocytopenia of the fetus]. *Post N Med.; 8*:628-634

Uhrynowska M, Niznikowska-Marks M, Zupanska B. (2000) Neonatal and maternal thrombocytopenia: incidence and immune background. *Eur J Haematol.; 64*:42-46

Wielgoś M., Szaflik K., Bartkowiak R. (2008). Konflikt serologiczny i choroba hemolityczna płodu [Serological conflict and hemolytic disease of the fetus]. special issue of *Ginekol. Dypl.*; 130-131.

Guz K., Orzińska A., Kopeć I., Krzemienowska M., Smolarczyk-Wodzyńska J., Brojer E. (2010). Aktualny stan i perspektywy nieinwazyjnejdiagnostyki prenatalnej w konfliktach matczyno-płodowych [Current State and Prospects for Noninvasive Prenatal Diagnostics for Maternal-Fetal Conflicts]. *Journal of Transfusion Medicine, vol. 3, no. 4, 144-154.*