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9

Red-cell and platelet alloimmunisation in pregnancy

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The management of red-cell alloimmunisation has been revolutionised by the widespread use of anti-D administration for mothers who are rhesus negative, and the availability of non-invasive, ultrasound-based techniques for reliable detection of moderate-to-severe fetal anaemia. With reduced frequency of alloimmunisation to the D antigen, antibodies to c and Kell antigen are increasingly responsible for red-cell alloimmunisation. Ultrasound-based, non-invasive diagnosis is now so reliable that invasive techniques are sparingly used to detect significant fetal anaemia. Treatment of fetal anaemia using ultrasound-guided intravascular transfusions is highly successful. Advances in molecular biology have led to the successful determination of fetal blood group using free fetal DNA from maternal blood. This development is highly likely to allow use of anti-D in only those pregnant women carrying rhesus-positive fetuses. Sensitisation to non-D group antibodies continues to occur owing to the lack of available prophylaxis for other blood-group antigens.

Introduction

Maternal red-cell alloimmunisation (also referred to as isoimmunisation) occurs when a woman's immune system is sensitised to foreign red-blood-cell surface antigens, leading to the production of immunoglobulin G (IgG) antibodies.

The most common causes of maternal sensitisation are blood transfusion or feto-maternal haemorrhage (i.e. transplacental passage of fetal red-blood cells) associated with childbirth, trauma,

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spontaneous or induced miscarriages, ectopic pregnancy or invasive procedures. The resulting antibodies often cross the placenta during pregnancies in sensitised women and, if the fetus is positive for the red-blood-cell surface antigens, this will lead to haemolysis of fetal red-blood cells and anaemia. This may result in potentially serious consequences for the fetus, such as hydrops fetalis and a high cardiac output failure syndrome.[1]

The rhesus blood-group system is the most common cause of maternal alloimmunisation (among more than 300 recognised blood-group antigens). It comprises the c, C, D, e and E antigens.[1] Alloimmunisation against rhesus antigens, leading to haemolytic disease of the fetus and newborn (HDFN) used to be a major cause of perinatal mortality, morbidity and long-term disability until the 1970s. Before the discovery of the rhesus system by Landsteiner and Weiner in 1940,[2] the mechanism of the disease was little understood. After this discovery, however, Levine et al[1] subsequently established that HDFN was usually caused by rhesus incompatibility. Furthermore, it was shown that rhesus alloimmunisation was caused by the passage of fetal rhesus D-positive red cells into the maternal circulation.[1]

The monitoring of pregnancies in which alloimmunisation was known to have occurred historically involved invasive testing, such as serial measurement of amniotic fluid optical density, which was shown to predict the severity of the disease.[3] Initial attempts to treat the condition *in utero* (in cases in which severe disease was predicted before fetal maturity) included intra-peritoneal transfusion and fetoscopy.[4,5] These which were replaced by ultrasound-guided cordocentesis and intra-vascular transfusion in the 1980s.[5] Attempts were also made to reduce the severity of the disease using techniques such as plasma exchange, but with limited success.[6]

One of the most important breakthroughs occurred in 1960 when administration of rhesus D IgG (also known as anti-D immunoglobulin or RhoGam) was shown to prevent rhesus-D alloimmunisation, Ultimately, this led to the licensing of anti-D and widespread use for prophylaxis.[1] Anti-D prophylaxis has greatly reduced the frequency of HDFN because of anti-D (which remains the most important cause of HDFN). Perinatal mortality resulting from rhesus disease has also decreased 100-fold in the past 3 decades.[2,7] Unfortunately, new immunisations continue to occur, with over 500 fetuses in England and Wales developing HDFN annually.[8]

Aetiology

Maternal alloimmunisation and fetal haemolytic disease is most commonly caused by the rhesus blood-group system. This system comprises the c, C, D, e, and E antigens. Importantly, there is no d antigen, and d refers to the absence of the D allele. The D antigen of the rhesus blood-group system remains the cause of the most severe cases of HDFN.

The development and implementation of antenatal rhesus D immune globulin prophylaxis has led to a significant reduction in the frequency of maternal anti-D antibodies, leading to a fall in the incidence of HDFN because of these antibodies. The different types of atypical antibodies found in maternal blood are presented in Table 1. The most severe cases of haemolytic disease in the fetus and newborn baby are caused by anti-D, anti-c, anti-E and anti-K antibodies.[9,10]

Sensitisation to non-D group continues to occur because of the lack of availability of antibody prophylaxis for other blood-group antigens. Consequently, the rate of HDFN related to these rarer antibodies is either stable or rising. In several Western countries with effective prophylaxis programmes, the combined frequency of these immunisations already exceeds the frequency of rhesus-D immunisation.[2]

Table 1
Association of atypical red cell antibodies and haemolytic disease of the fetus and newborn.[1]

Common	D, anti-Kell, c, E
Uncommon	Anti e, C, cE, Ce, C^w, Kp^a, Kp^b, k, Jk^a, s, Wr^a, Fy^a
Rare	Biles, Co^a, Di^a, Di^b, Do^a, En^a, Fy^b, Good, Heibel, Jkb, Lu^a, Lu^b, M, Mi^a, Mt^a, N, Radin, S, U, Yt^a, Zd
No documented cases	Le^a, Le^b, P