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Review

Management of red blood cell alloimmunization in pregnancy

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ABSTRACT

The main cause of fetal anemia is maternal red blood cell alloimmunization (AI). The search of maternal antibodies by indirect antiglobulin test allows screening for AI during pregnancy. In case of AI, fetal genotyping (for Rh-D, Rh-c, Rh-E and Kell), quantification (for anti-rhesus antibodies) and antibody titration, as well as ultrasound monitoring, are performed. This surveillance aims at screening for severe anemia before hydrops fetalis occurs. Management of severe anemia is based on intrauterine transfusion (IUT) or labor induction depending on gestational age. After intrauterine transfusion, follow-up will focus on detecting recurrence of anemia and detecting fetal brain injury. With IUT, survival of fetuses with alloimmunization is greater than 90% but 4.8% of children with at least one IUT have neurodevelopmental impairment.

Introduction

The main cause of fetal anemia is maternal red blood cell alloimmunization (AI). This review describes the pathophysiological mechanisms of AI and the diagnostic, therapeutic and surveillance procedures to be followed.

Epidemiology

Maternal red blood cell alloimmunization is a rare pathology of pregnancy. About 1–2 in 1000 women are immunized [1]. Despite preventive measures that have been in place for more than 30 years, the most frequent immunization is against Rh-D (RH1) with 6 cases per 1000 live births in the USA and approximately 750 cases per year in France (88% of immunizations) [1,2]. The other most common anti-erythrocyte antibodies are anti-Rhc (RH4), anti-RhE (RH3) and anti-Kell (KEL). Maternal red blood cell alloimmunization is the leading cause of fetal anemia. Prenatal consequences vary tremendously depending on the type of antibody, quantification and affinity for the corresponding antigen, ranging from lack of significant impact to hydrops fetalis or intrauterine fetal death.

Physiopathology

Maternal red blood cell alloimmunization results from the production of immunoglobulin G (IgG) maternal antibodies against erythrocyte surface antigen that she lacks (primary immune response). Immunization is most often secondary to fetal-maternal hemorrhage and more rarely to transfusion or needle exchange in drugs addicts [2,3].

Some particular situations, such as miscarriage, abortion, trauma, invasive prenatal diagnosis, childbirth, may contribute to fetal-maternal hemorrhage but it may also occur spontaneously. On reexposure to antigen, usually during a subsequent pregnancy, a secondary immune response occurs with rapid synthesis of IgG antibodies. IgG antibodies cross the placental barrier, bind to the fetal red blood cells – if they have the corresponding antigen – and are therefore responsible for progressive fetal hemolytic anemia.

Fetal consequences are all the more important as the rate and affinity of antibodies for antigens are high. The type or specificity of the antibody is also essential. Some antibodies have no fetal

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incidence, while others will cause severe fetal anemia. There is no risk for autoantibodies (anti-Lewis and anti-P1 for example). It is limited to neonatal jaundice for anti-E, and anti-Cw. Finally, severe fetal damage is possible for anti-RhD, anti-c and anti-Kell (Table 1).

In the fetus, hemolysis is initially compensated by an increase in medullary and extra-medullary erythropoiesis (liver and spleen) that is responsible for hepatosplenomegaly, which induces portal hypertension and decreased hepatic protein synthesis capacity [4]. This leads to hypoproteinemia and hypoalbuminaemia, which contribute to the development of edema and ascites when anemia is severe. The decrease in oxygen content due to anemia triggers hemodynamic compensatory mechanisms (increased fetal cardiac output, redistribution of blood flow to the heart and brain), with the aim of maintaining oxygen supply at the myocardial and cerebral levels. In case of aggravating anemia, heart failure can occur and thus contribute to occurrence of hydrops fetalis.

Progressive anemia is well tolerated especially during the first part of pregnancy. In case of severe anemia, the hemodynamic compensatory mechanisms are outplayed with the appearance of functional hydrops fetalis at first and then entailing irreversible lesions.

In anti-Kell alloimmunization, the mechanism leading to fetal consequences is more complex. Fetal hemolysis is worsened by direct inhibition of erythropoiesis by the anti-Kell antibodies [5].

At birth, maternal antibodies persist several weeks in the newborn's blood flow and so does the risk of anemia. Hemolysis is responsible for a release of bilirubin causing neonatal jaundice with sometimes severe consequences. In fact, the bilirubin released by the haemolysis is liposoluble therefore potentially neurotoxic with the risk of kernicterus in case of accumulation in children, which is the gravity of hyperbilirubinemia by hemolysis [4].

Management of alloimunization during pregnancy

Screening for AI during pregnancy is performed searching for the presence of maternal antibodies by indirect antiglobulin test (Fig. 1). Indirect antiglobulin test is compulsory during pregnancy (Decree of 14/02/1992 in France). It must be systematic at the first prenatal consultation regardless of the mother's Rhesus. In case of positive indirect antiglobulin test during pregnancy (and provided there has been no recent anti-D immunoglobulin injection in case of anti-D positive indirect antiglobulin test), the diagnosis of maternal red blood cell alloimmunization can be made and specific management is required. On discovery of alloimmunization, investigating patient's AI history, characterizing the type of antibodies and checking whether the fetus has the corresponding antigen or not, should assess the risk of fetal anemia.

In order to determine whether the fetus carries the corresponding antigen for the maternal antibody, it is possible to first perform paternal phenotype. If the father is homozygous for the antigen corresponding to the maternal antibody, the risk of incompatibility is 100%, whereas if he is heterozygous, the risk is 50%. Knowledge of paternal zygosity is acquired directly by the paternal erythrocyte study, except in case of *Rh-D* gene, because serological recognition of allele d is impossible [3].

In case of paternal heterozygosity or anti-RhD AI, fetal genotyping from maternal blood may be prescribed [6]. This technique was developed in the 2000s after Lo et al., in 1997, demonstrated that 1 to 6% fetal DNA was present in maternal plasma. It is currently possible for Rh-D, Rh-c, Rh-E and Kell. Noninvasive fetal Rh-D genotyping was validated by a French 2004 study of 851 pregnant women from 12 weeks of gestation [7]. Recently, Vivanti et al. showed the excellent efficacy of this screening on 416 Rh-D negative maternal serums in the first quarter of pregnancy with a sensitivity of 100% [95% CI (96.9–100)], a specificity of 95.2% [95% CI (95.5–97.6)], a positive predictive value (PPV) of 97.1% [95% CI (94.2–98.6)] and a negative predictive value (NPV) of 99.8% [95% CI (100)] [8]. In 2.2% of cases, fetal genotyping was indeterminate, which could have been accounted for by the high proportion of African women in these cases (6 on 9 cases) [8].

Since 2010, KEL genotyping is possible by allele-specific typing (KEL1 typing). It was validated on 47 genotypes performed in pregnant women with KEL:-1 phenotype with 100% PPV and NPV. The conditions for KEL genotyping must be rigorous because of analysis difficulties [9]. The first results for Rh-c and Rh-E genotyping have been encouraging with detection rates of 96.2% and 98.2%, respectively [10].

With positive genotyping, specific and close monitoring should be implemented to detect fetal anemia. If it is negative, a second sampling is necessary in order to eliminate a false negative and then monitoring can be less intense. Fetal risk level also depends on antibody production rate and antibody affinity for antigen. Antibody titration is the in vitro measurement by an indirect Coombs test of the amount of antibodies able to bind to red blood cells. The antibody titer corresponds to the inverse of the last dilution giving a positive reaction. It should be done every 15 days after 16 WG. In case of Kell alloimmunization, titers should be monitored once a month during pregnancy. There is a risk of fetal anemia from a titer greater than 1/16 [3].

Quantification measures the real antibody concentration. It is only possible for anti-Rhesus antibodies. It must be performed from titer $> 1/8$. There is a risk of fetal anemia if quantification is greater than 1 μg/mL [3] [1 μg/mL = 5 IU = 250 U Center for Perinatal Hemobiology (CHP)] for RH1 (D) and if quantification is greater than 500 UCHP for RH3 and RH4 [11].

Once the risk of fetal anemia has been estimated according to the various parameters described, ultrasound monitoring is required. It is based on measurement of middle cerebral artery peak systolic velocity (MCA-PSV) and on search for signs of hydrops fetalis. For patients with high-titer antibodies from the beginning of pregnancy or Kell alloimmunization, ultrasound monitoring can be started as early as 16 weeks of gestation. It can

Table 1
Antigens involved in fetal anemia. French National Center for Perinatal Hemobiology (CNRHP).

Specificity (traditional nomenclature)	Specificity (numerical nomenclature)	Risk for fetal anemia
Anti-D	Anti-RH1	YES after 15 WG
Anti-c	Anti-RH4	YES after 20 WG
Anti-kell	Anti-KEL1	YES after 15 WG
Anti-E	Anti-RH3	RARE (3rd quarter)
Anti-e	Anti-RH5	Exceptional
Anti-Fya	Anti-FY1	Exceptional
Anti-Jka	Anti-JK1	Exceptional
Anti-Kpa	Anti-KEL3	Exceptional
Anti-M	Anti-MNS1	Exceptional

WG: week of gestation.

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