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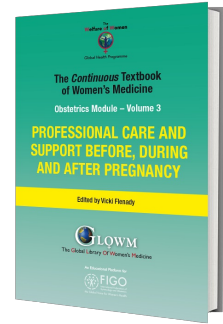
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Chapter

Prevention of Rhesus Alloimmunization

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ALLOIMMUNIZATION AND PERINATAL HEMOLYTIC DISEASE

Hemolytic disease of the fetus and newborn (HDFN) is characterized by maternal–fetal blood incompatibility and consequent anemia provoked by maternal antibodies against the erythrocyte antigens of the fetus. When the erythrocyte antigens invade organisms that do not contain them, an immune response is triggered, which culminates in the formation of specific antibodies, a phenomenon called immunization. Alloimmunization is the immune response to an antigen of the same species, and accounts for all events of HDFN.¹ In the past, perinatal mortality in alloimmunized pregnancies reached 50%, and HDFN accounted for about 10% of the causes of fetal and neonatal deaths. Medical advances during the past century have revolutionized the understanding of this serious condition and promoted a significant reduction of its occurrence, morbidity and mortality,² although it remains a public health problem in developing countries.²

ERYTHROCYTE ANTIGENS

The number of fetal erythrocyte antigens is vast. Due to their high prevalence and immunological characteristics, Rhesus (Rh) system antigens are the most important in the context of HDFN. They are located on the short arm of chromosome 1 and can be grouped into three pairs: Dd, Cc and Ee. The pair Dd is the most important, since it has the greater antigenic power, and approximately 55% of individuals are heterozygous for the D locus.³ There are variants of D antigen, called partial D (some epitopes of antigen D absent), weak D (weakly expressed D antigen epitopes), Rh mod and D (el), which may or may not present as D positive in serological reagents. Patients carrying these variants are potentially at risk of developing anti-D antibodies⁴ and will need prophylaxis if not previously sensitized.⁵

The prevalence of Rh-negative people is 15% in caucasians, 4–8% in black populations and 1–2% in Asians and native

Americans. It is interesting to note that 30–35% of the Basque population in France and Spain are Rh-negative.³

INCIDENCE OF ALLOIMMUNIZATION

The incidence of Rh alloimmunization changed after the development of anti-D immunoglobulin prophylaxis. In US, where prophylaxis is universal, data from the National Center for Health Statistics in 2003 reported an incidence of HDFN in 6.8 of 1000 live births. In the UK, it is estimated that HDFN occurs once every 21,000 live births. However, in poorer and developing countries the benefits of prophylaxis are still not fully recognized owing to the unavailability of the drug or to the lack of adequate protocols to address this condition.⁶

PROPHYLAXIS OF RhD ALLOIMMUNIZATION

The investigation of indirect maternal Coombs' test is the first step to identify pregnant women susceptible to alloimmunization and those already alloimmunized. All pregnant women (D-negative or D-positive) should be screened at the first appointment for antibodies with the indirect anti-globulin test (indirect Coombs' test).⁵ There is no consensus whether screening should be repeated at 28 weeks to identify the 0.18% of pregnant woman that alloimmunize during gestation.

When paternity of the infant is assured, the Rh-negative woman's partner must undergo Rh typing to eliminate unnecessary administration of blood product if he is also Rh-negative.⁷

DNA analysis can determine the heterozygosity of the paternal genotype and, in these cases, it is still possible for the fetus to be Rh negative. Since maternal plasma contains a large amount of free fetal DNA, it has been possible to determine the RhD genotype of the fetus in a non-invasive manner. However, this type of analysis is not systematic or recommended even in developed countries.⁸

PREVENTION

Prophylaxis of alloimmunization by Rh (D) antigen is performed by administration of anti-Rh (D) immunoglobulin [IgRh (D)]. Polyclonal preparations derived from human plasma through Cohn's cold ethanol fractionation can only be given intramuscularly because this process can result in contamination with plasma proteins and IgA, possibly leading to severe hypersensitivity and anaphylactic reactions if administered intravenously.

Owing to being obtained from the plasma of alloimmunized persons, IgRh (D) can transmit diseases, such as hepatitis C and HIV. For this reason, monoclonal anti-D antibodies are under investigation and may replace the polyclonal products derived from human plasma.

Immunoglobulin administration is indicated in the postpartum period of Rh-negative, non-sensitized women (negative indirect Coombs' test) whose neonate is Rh-positive. Gestational prophylaxis is also indicated for events that increase the risk of fetal–maternal hemorrhage, such as:

1. Abortion;
2. First trimester bleeding;
3. Hydatidiform mole pregnancy;
4. Ectopic pregnancies;
5. Invasive procedures (chorionic villus sampling, amniocentesis, fetal surgery);
6. Stillbirth;
7. Hemorrhages of the second and third trimesters;
8. Abdominal trauma;
9. External version.

IgRh (D) (300 µg) should be administered within 72 hours after delivery, although some efficacy is reported up to 28 days postpartum.

Following administration of IgRh (D), antibody screening gives poorly reactive, low titer results. It is important to note that IgRh (D) crosses the placenta and binds to fetal blood without causing hemolysis, although there are rare reports of fetal anemia related to the use of anti-D immunoglobulin.

Adverse reactions are rare and usually mild, such as local swelling, headache and chills. Hypersensitivity reactions, such as urticaria, itching and maculopapular rash that do not respond to antiallergic drugs are also very uncommon. Although the occurrence of anaphylaxis after the use of anti-D IgG immunoglobulin is very rare, it is recommended to have ready a solution of adrenaline.

If the RhD-negative pregnant woman does not receive anti-D IgG prophylaxis after the birth of a RhD-positive infant, the incidence of sensitization during pregnancy will be 12–16%. The rate of sensitization when prevention after birth is performed is 1.6–1.9%, while antenatal prophylaxis reduces the rate of sensitization during pregnancy to 0.2%.⁹

After administration of anti-D immunoglobulin, it is possible to estimate whether the standard dose has been sufficient to neutralize fetal cells in maternal circulation through a fetomaternal hemorrhage (FMH) test. However, there is no evidence to recommend or contraindicate the routine use of the postpartum FMH test even before 12 weeks of pregnancy.

RhD-negative pregnant woman sensitized to other blood group antigens (non anti-D) should receive prophylaxis for the same indications as patients with negative Coombs' indirect test.⁵

ROUTINE ANTENATAL PROPHYLAXIS WITH ANTI-D IMMUNOGLOBULIN

Administration of antenatal immunoglobulin is recommended by most authors. In order to prevent spontaneous sensitization during pregnancy, especially in the third trimester, in the US it is recommended the use of 300 µg at the 28th gestational week,⁵ in the UK, France, Australia, Cuba and Canada the recommended dose is of 100 µg of IgRh (D) at 28 and 34 weeks.

The incorporation of fetal genotyping into clinical practice may also change the use of prophylaxis protocols, with them being reserved for antenatal IgRh (D) for Rh-positive or unknown fetuses. Another future possibility is the production of anti-Rh (D) immunoglobulin through genetic engineering, which would reduce the cost and remove the inherent risks of a blood product.

PRACTICE RECOMMENDATION

- All pregnant women should be screened at the first appointment for antibodies with the indirect anti-globulin test (indirect Coombs' test). There is no consensus whether screening should be repeated at 28 weeks to identify the 0.18% of women who undergo alloimmunization during gestation.
- When paternity of the infant is assured, the Rh-negative woman's partner must undergo Rh typing to eliminate unnecessary administration of blood product.
- 300 µg of anti-D IgG should be used within 72 hours of delivery for non-sensitized Rh-negative women with Rh-positive newborns.
- If anti-D immunoglobulin was not used within 72 hours of birth or any potentially sensitizing event, it may be used for up to 28 days with some protective effect.
- There is insufficient evidence to recommend or contraindicate the routine use of the postpartum fetomaternal hemorrhage (FMH) test.
- Most protocols recommend that anti-D IgG should be given to non-sensitized Rh-negative women at 28 weeks of gestation when the fetal blood group type is Rh-positive or unknown.
- After abortion, ectopic or molar pregnancy there is an indication for anti-D in non-sensitized Rh-negative women: 120 µg up to 12 weeks and 300 µg after.
- Anti-D should be used after molar pregnancy in Rh-negative women not sensitized.
- A dose of 300 µg anti-D should be administered after amniocentesis and cordocentesis in non-sensitized Rh-

negative women.

- **In chorionic villous sampling, the recommended anti-D dose is 120 µg in the first 12 weeks of gestation and 300 µg after that in non-sensitized Rh-negative women.**
- **Informed consent, verbal or written, must be obtained prior to administration of Rh immunoglobulin as any blood product.**
- **When the lowest fractionated dose is not available, use the dose of 300 µg that is most widely available.**

CONFLICTS OF INTEREST

The authors of this chapter declare that they have no interests that conflict with the contents of the chapter.

CURRENT GUIDELINES

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 192 Summary: Management of Alloimmunization During Pregnancy. 2018.

British Society of Haematology. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. 2014.

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