CIESIELSKI, Radoslaw, MICH, Anna, PERKOWSKA, Klaudia, KAŹMIERCZAK, Anna, IZDEBSKA, Wiktoria, SORNEK, Patrycja, BORKOWSKA, Agata, KIEŁB, Anna, PAWLAK, Igor and STANEK, Jakub. RhD alloimmunization – diagnostics, therapy and prophylaxis. Quality in Sport. 2024;32:56059. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.32.56059
https://apcz.umk.pl/QS/article/view/56059

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 08.11.2024. Revised: 13.11.2024. Accepted: 02.12.2024. Published: 02.12.2024.

RHD ALLOIMMUNIZATION – DIAGNOSTICS, THERAPY AND PROPHYLAXIS

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Abstract

Introduction:

The success in preventing and treating Rh D alloimmunization is a major accomplishment in modern obstetrics. The widespread use of Rh D immune globulin has led to a decline in red cell alloimmunization. Despite evidence of its effectiveness, many cases of Rh D alloimmunization persist due to non-compliance with established protocols. Implementing routine anti-D prophylaxis (RAADP) during the third trimester is well-established but requires more careful.

Aim of study:

The aim of the study is to summarize the available knowledge about alloimmunization in pregnancy and methods of prophylaxis. The definition, patomechanism, methods of treatment and prophylaxis were summarized and described.

Materials and methods:

The literature available in PubMed database was reviewed using following keywords: "alloimmunization in pregnancy", "serological conflict", "fetal anemia", "HDFN", "prophylaxis of alloimmunization".

Conclusion:

Advancements in diagnosing, treating, and preventing hemolytic disease of the fetus and newborn are notable. Quick, non-invasive diagnostics have facilitated more efficient treatment implementation. Prevention methods include specific and nonspecific prophylaxis, which can start during or after pregnancy. Numerous guidelines and studies exist regarding immunoglobulin use in pregnancy. However, medical staff education on managing hemolytic disease during pregnancy is crucial.

Keywords: alloimmunization in pregnancy, serological conflict, fetal anemia, prophylaxis

Introduction

Progress in preventing and treating Rh D alloimmunization stands out as one of modern obstetrics' significant achievements. Historically, the fetal effects of maternal red blood cell (RBC) alloimmunization were undetectable until after the birth of an affected infant. The widespread utilization of Rh D immune globulin has contributed to the decreased incidence of red cell alloimmunization in economically advanced nations.

Despite substantial evidence of effectiveness, a significant number of cases of Rh D alloimmunization persist due to non-compliance with established protocols.

The routine use of anti-D prophylaxis (RAADP) to prevent Rhesus (Rh) D alloimmunisation during the third trimester is well established and requires careful and well-audited local implementation to achieve the maximum public health benefit.

Definition and patomechanism

Maternal-fetal serological conflict is a condition in which, due to an antigenic incompatibility between the red blood cell antigens of the mother and the fetus, the pregnant woman's body produces immune antibodies directed against fetal antigens. Alloantibodies traverse the placenta and opsonize fetal red blood cells (RBCs), which are then removed by the mononuclear phagocyte system of the fetus. The heme component of hemoglobin in the phagocytosed fetal RBCs is converted to bilirubin, which can pass into the brain interstitium causing irreversible neural damage with dire consequences for the child. This neurological condition is referred to as kernicterus [1], which most commonly affects the nuclear regions of the brain, such as the basal ganglia, the hippocampus, the geniculate bodies, and the cranial nerve nuclei [2]. This results in hemolytic disease of the fetus and/or newborn, the main symptom of which is severe hemolytic anemia. This can lead to chronic intrauterine hypoxia, causing damage to fetal tissues and organs, generalized edema, and ultimately fetal death [1].

Immunization, or sensitization, of the mother to fetal antigens typically happens when fetal blood with foreign antigens interacts with the mother's immune system. While the placenta theoretically acts as a barrier to prevent this, it can fail, particularly when the integrity of the chorion or placenta is compromised (e.g., during childbirth, miscarriage, ectopic pregnancy surgery, invasive intrauterine procedures, bleeding, or injuries). Immunization can also occur through non-pregnancy-related means, such as incompatible blood transfusions or repeated use of contaminated injection equipment [2].

Upon recognizing foreign red blood cell antigens, the pregnant woman's body mounts a primary immune response, producing IgM antibodies that do not cross the placenta, posing no threat to the fetus. However, with subsequent exposure to the antigen, usually in a later pregnancy, the memory immune response is activated, resulting in the production of IgG antibodies. These IgG antibodies can cross the placenta through active transport, bind to the antigen, coat the erythrocytes, and initiate the cascade of events leading to the condition described [1].

Approximately 43 of the 300 RBC antigens listed by the International Society of Blood Transfusion reportedly cause HDFN, but some are more likely to be associated with hemolysis than others [3].

It has long been known that anti-D antibodies are the most likely RBC alloantibodies to cause severe HDFN [4]. Studies have shown that the combination of anti-D with another antibody can have a synergistic effect and cause a more severe form of HDFN [5]. Since the implementation of RhIg prophylaxis, there has been a shift toward other alloantibody specificities, including antibodies against Kell (K) and other Rhesus antigens, especially c [6].

Diagnosis

At-risk pregnancies are identified based on a previous history of Hemolytic Disease of the Fetus and Newborn (HDFN) or when causative antibodies are detected during routine maternal blood group screening [4]. If paternity is certain, the initial management involves determining the father's RBC antigen status and zygosity.

If the father is heterozygous for a specific RBC antigen, the fetus has a 50% chance of inheriting it, and fetal genotyping can be performed. If the father is homozygous, all fetuses will inherit that antigen, making genotyping unnecessary. Fetal RhD genotype can now be accurately determined using cell-free DNA in maternal plasma, with prediction accuracy and test sensitivity approaching 100% and very few false negatives [7]. The International Blood Group Reference Laboratory in Bristol, UK, performs genotyping for RHD, RHC, and RHE after 16 weeks and for Kell after 20 weeks of gestation [8]. In sensitized pregnancies, serial antibody titers are measured, typically every 4 weeks until 28 weeks of gestation and then every 2 weeks thereafter. In the past, once titers reached a critical level indicative of high risk for fetal anemia, fetal anemia detection in red cell alloimmunization cases was based on spectrophotometric measurement of amniotic fluid bilirubin concentration
[9].

Doppler assessment of the middle cerebral artery peak systolic velocity (MCA-PSV) has shown higher sensitivity and accuracy (also being a non-invasive technique) for predicting severe fetal anemia in Rh-alloimmunized pregnancies compared to amniotic fluid ΔOD450 [10]. Once critical antibody titers are reached, MCA-PSV is assessed to determine the optimal timing for fetal blood sampling (FBS) [2]. Values from 1.5 MoM and above highly suggest the presence of severe fetal hemolytic disease. Vascular flow studies should begin at 18 weeks of pregnancy. If the results indicate the absence of severe hemolytic disease, the tests should be repeated every 1 to 3-4 weeks, depending on the current situation [4]. It is crucial that Doppler studies are performed according to established guidelines, ensuring they are highly reliable and reproducible.

Diagnosis testing for the presence of immune antibodies to red blood cell antigens (indirect antiglobulin test, Coombs test) must be performed on every pregnant woman at the beginning of pregnancy [6]. This should be a mandatory test. If the pregnant woman is Rh-positive, the diagnostic process ends if the result is negative. For Rh-negative women, further tests are conducted in each trimester of pregnancy. If antibodies are detected, they must be identified, and their titer determined. However, it should be noted that the antibody titer correlates poorly with the degree of fetal anemia, especially in subsequent conflict pregnancies [2].

Patients with a high antibody titer (defined as any value exceeding 1:16) or with a history of severe forms of hemolytic disease should be quickly assessed to determine if hemolytic disease has developed in the current pregnancy and to examine its potential severity [8].

Therapy

In cases of abnormal MCA-PSV values indicative of severe fetal hemolytic disease, it is essential to initiate intrauterine therapy by transfusing donor's blood into the fetoplacental circulation. Most commonly, exogenous blood is administered into the umbilical vein, less frequently into fetal vessels, and in exceptional cases, directly into the heart [11]. The fetal liver and placental cord insertion are considered the safest sites, while puncture of a free loop seems to have a higher complication rate [8, 12]. Fetal paralysis with atracurium, vecuronium, or rocuronium should be considered, and the drug can be delivered either intramuscularly, intraperitoneally or directly into the umbilical vein [8]. Fetal paralysis minimizes the risk of needle displacement caused by fetal movements and can reduce complications such as arterial spasm, cord hematoma, or excessive bleeding from puncture site tears.

This approach is especially beneficial for procedures conducted at advanced gestational ages or those anticipated to be lengthy. A recent large series involving 1678 intrauterine transfusions (IUTs) demonstrated that the routine use of fetal paralysis was associated with improved outcomes [13]. Intra-abdominal transfusions are now rarely used, except when fetoplacental vessels are inaccessible, often due to a very early gestational age [8]. In case of the intrafetal transfusion the analgetic factors reducing fetal pain are strongly recommended.

IUT is usually performed with fresh donor red blood cells, 0-negative, Kell-negative, CMVnegative, washed, irradiated, leukocyte depleted, and packed to a hematocrit of 75-80%. Obviously, the blood is negative for the antigens against which the mother is eventually immunized and often is checked for other antigens (e.g., Duffy, Kidd, MNS and other blood groups) against which she may develop antibodies [14].

The volume of blood to be transfused depends on donor and fetal pretransfusion and target Hb/hematocrit. Moreover, when transfusing large volumes of blood, it is common practice to obtain a sample during the second half of the transfusion to avoid unnecessary overload [12].

There is no strong evidence on the optimal timing for delivering a fetus that has undergone intrauterine transfusions (IUTs). The goal is to deliver a near-term neonate with either no anemia or moderate anemia, avoiding the need for exchange transfusions or extended phototherapy. In cases of maternal alloimmunization with a stable fetus that has received multiple IUTs, most clinicians recommend a final transfusion no later than 34-35 weeks, aiming for delivery at 36-37 weeks [8, 12, 15]. Several complications can affect IUT, namely, rupture of membranes, infection, bleeding from the puncture site, cord hematoma leading to vessel compression, bradycardia, or tachycardia [12].

Intravenous immunoglobulin (IVIG) therapy may be beneficial in cases of HDFN, as it saturates the Fc-mediated transplacental transport of IgGs, reduces maternal Ig production, and potentially decreases the macrophagic uptake of opsonized RBCs in the fetus [12]. While IVIG might reduce hemolysis, it does not address fetal anemia [16], suggesting its potential role is in preventing or delaying anemia in high-risk HDFN pregnancies. Treatment with IVIG, alone or combined with therapeutic plasma exchange, might lower the risk of hydrops and fetal death in severely Rh-sensitized patients [17]. However, more robust evidence is required before IVIG can be widely recommended, given its high cost and potential complications.

PREVENTION OF ALLOIMMUNIZATION

Nonspecific and specific prophylaxis

Nonspecific prophylaxis involves adhering to transfusion principles, avoiding unnecessary blood contact, and using only single-use injection equipment—simple measures that help prevent all forms of serological conflict. The most crucial role is played by specific prophylaxis, which involves the use of anti-D immunoglobulin in certain situations. This approach has significantly reduced the incidence of the most common serological conflict, which is based on RhD antigen immunization, over recent decades.

The routine use of Rh D immune globulin has significantly lowered the rate of red cell alloimmunization in more economically developed countries. Initially introduced in the 1970s, postpartum administration of Rh D immune globulin decreased the alloimmunization rate in atrisk pregnancies from about 13–16% to roughly 0.5–1.8% [18, 19].

This risk was further minimized to 0.14–0.2% with the implementation of routine antepartum administration [18, 19]. Despite strong evidence of its efficacy, many cases of Rh D alloimmunization still occur due to non-compliance with established protocols. Additionally, new data have emerged to aid in the management of cases, particularly concerning women with the weak D phenotype. Anti-D immune globulin is produced through cold alcohol fractionation of plasma donated by individuals with high levels of anti-D immune globulin G antibodies. Research from the 1960s demonstrated that maternal sensitization to Rh-positive fetal blood could be prevented by administering anti-D immune globulin. A prophylactic dose of 300 micrograms (1500 IU) of anti-D immune globulin is effective in preventing Rh D alloimmunization after exposure to up to 30 mL of Rh D-positive fetal whole blood or 15 mL of fetal red blood cells [20].

Anti-D immune globulin is collected through apheresis from volunteer donors with high levels of circulating anti-Rh D antibodies. The donated plasma is pooled and processed by commercial manufacturers to produce anti-D immune globulin in various doses. In the 1990s, concerns emerged about the future supply of anti-D immune globulin to meet global demand, as the number of potential donors might decrease [21]. Experts in the United Kingdom at that time estimated that the supply would be insufficient to provide immunoprophylaxis for all at-risk Rh D-negative women if standard recommendations were followed [22]. A shortage in Australia in 1995 led to the importation of anti-D immune globulin. As a result, some physicians suggested limiting the doses for first-trimester indications and discontinuing administration after external cephalic version (unless fetal-maternal hemorrhage was confirmed), ectopic pregnancy, or threatened miscarriage [23]. However, others argued that it was unethical to withhold anti-D immune globulin in any situation. Future supply estimates for the United States have not been published, and no supply shortages have been reported since these concerns were raised two decades ago. Despite these earlier worries, national guidelines in the United States, United Kingdom, and Canada still recommend routine administration of anti-D immune globulin to all Rh D-negative nonsensitized women in the third trimester (28-30 week of gestation), within 72 hours of delivering an Rh-positive infant, or following a sensitizing event (e.g., ectopic pregnancy, external cephalic version, or invasive obstetric procedures such as chorionic villus sampling or amniocentesis) [24, 25, 26].

Post-pregnancy prophilaxis

Traditional postpartum immunoprophylaxis involves administering anti-D immunoglobulin after the end of pregnancy—following childbirth, miscarriage, or ectopic pregnancy surgery—situations where there is an increased risk of fetomaternal hemorrhage [22]. Ideally, this should be done within 72 hours of the actual or potential hemorrhage, but if this is not possible (e.g., due to the unavailability of immunoglobulin), it should be administered as soon as possible, within a maximum of 10 days [22]. Administering immunoglobulin beyond this period is no longer effective and thus not justified.

The dose of immunoglobulin depends mainly on the expected volume of fetomaternal hemorrhage, which is primarily determined by the gestational age. In Poland, standard doses range between 50 and 450 mcg (250 – 2250 IU) of anti-D immunoglobulin.

More effective prophylaxis can be achieved by using individually tailored doses based on the actual volume of fetomaternal hemorrhage, but this approach requires assessing the size of the hemorrhage each time (using the Kleihauer-Betke test or flow cytometry) [22].
Postpartum prophylaxis should be administered to all Rh D-negative women who have given birth to an Rh D-positive child (or if the Rh D status is unknown, for example, due to very early gestational age). An absolute requirement is the absence of maternal immune antibodies, as evidenced by a negative indirect Coombs test [22].
According to the guidelines proposed in medical centers in Poland, anti-Rh D immunoglobulin is administered intramuscularly to Rh D-negative women as follows:

1. After the birth of an Rh D-positive child:
    a. 150 mcg (750 IU) if the delivery was physiological
    b. 300 mcg (1500 IU) if the delivery was pathological, e.g., cesarean section, stillbirth, multiple birth, Credé's maneuver, or manual removal of the placenta.
2. After spontaneous miscarriage or termination of pregnancy, invasive prenatal diagnostics (amniocentesis, chorionic villus sampling, cordocentesis), removal of an ectopic pregnancy, in case of threatened miscarriage or preterm delivery accompanied by vaginal bleeding, and after external cephalic version:
    a. 50 mcg (250 IU) up to the 20th week of pregnancy
    b. 150 mcg (750 IU) after the 20th week of pregnancy

Anti Rh D immunoglobulin is not administered in the case of a complete spontaneous miscarriage up to the 12th week of pregnancy (without uterine curettage) that occurred without severe pain. In such cases, the duration of pregnancy should be documented by an ultrasound examination [20]. In the situation of recurrent bleeding during pregnancy, consideration should be given to administering a standard dose of immunoglobulin every 6 weeks [22].
Women who exhibit a weak expression of the D antigen, classified as weak D type 1, 2, or 3, determined by the alleles RHD01W.1, RHD01W.2, and RHD*01W.3, are designated as Rh Dpositive. These individuals are not prone to producing anti-D antibodies and are not eligible for anti-D immunoglobulin administration. Other weak variants of the D antigen are classified as Rh D-negative.

In-pregnancy prophilaxis

An excellent complement to traditional postpartum prophylaxis is the so-called antenatal prophylaxis, which involves administering anti-D immunoglobulin to all RhD-negative pregnant women with a negative indirect antiglobulin test result, between the 28th and 30th weeks of pregnancy [22]. This procedure prevents sensitization during the final weeks of pregnancy. In some women, especially in the third trimester, minor fetomaternal hemorrhages may occur, which can sometimes cause sensitization [8]. Unfortunately, it is impossible to determine in which women or when this might happen, hence the need to provide prophylaxis to all women who meet the mentioned criteria. The dose of immunoglobulin used in antenatal prophylaxis is 300 mcg (1500 IU) [22].
In the United States, recommendations for administering anti-D immune globulin were introduced in the 1970s. The current practice involves giving a single antenatal dose of 300 micrograms of anti-D immune globulin at 28 weeks of gestation, followed by a second dose after birth if the newborn is identified as Rh positive.

This protocol, based on recommendations from a 1977 conference at McMaster University, has resulted in an Rh alloimmunization rate of less than 0.2% [27, 28]. In the United Kingdom, the guidelines differ slightly: anti-D immune globulin may be administered as two injections at 28 and 34 weeks of gestation, or as a single dose at 28 weeks [29, 30]. There are no trials comparing the efficacy of the single-dose regimen to the two-dose regimen, and no evidence suggests a difference in effectiveness [29]. However, an observational study in the UK found better adherence to the single-dose protocol compared to the two-dose regimen [31], and the single-dose approach may also reduce costs [32]. Consequently, there is no strong evidence to suggest switching from the single-dose regimen used in the United States to a two-dose regimen.

It is essential to remember that the administration of antenatal immunoprophylaxis does not exempt us from repeating it after pregnancy ends – the standard dose of the preparation should be given to all Rh D-negative women who have given birth to an Rh D-positive child, but without performing the indirect antiglobulin test, as its result could be falsely positive due to the prior administration of immunoglobulin during pregnancy [22].

Rh alloimmunization can still occur during pregnancy in Rh D-negative women. This may result from failing to administer antenatal prophylaxis in the third trimester, inadequate dosage, or delays in administering anti-D immune globulin within 72 hours after a known sensitizing event during pregnancy or after birth, or from unrecognized fetal-maternal hemorrhage at some point during pregnancy [33]. Despite immunoprophylaxis recommendations, approximately 0.1–0.4% of at-risk women become sensitized during pregnancy [34]. A recent retrospective study from New Zealand identified several reasons for continued sensitization cases, including the omission of immune globulin after a recognized sensitizing event in 41% of cases and administration outside the recommended guidelines in 13% of cases [35]. Additionally, there is a small rate (0.1–0.2%) of spontaneous immunization despite adherence to the recommended prophylaxis protocol [33]. These cases often occur in pregnancies without any prior overt sensitizing events, indicating that prophylaxis is not 100% effective [36].

Conclusion

Currently, the diagnosis, therapy, and prevention of hemolytic disease of the fetus and newborn have significantly advanced, particularly in developed countries. Rapid, non-invasive, and widely available diagnostics have greatly facilitated the more efficient implementation of treatment for the adverse effects of hemolytic disease. Current therapeutic methods are effective and carry low risk but depend on the skills of the physician and the availability of medical equipment. Prevention of hemolytic disease is divided into specific and nonspecific prophylaxis. Nonspecific prophylaxis can be initiated during pregnancy or after its completion. There are many guidelines, studies, and recommendations regarding indications, methods, and possibilities of using immunoglobulin during pregnancy. However, attention should be paid to the education of medical personnel regarding diligence in managing diagnosed cases of hemolytic disease during pregnancy.

Supplementary materials
Not applicable.

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Conceptualization, Radosław Ciesielski and Anna Mich, methodology, Klaudia Perkowska, software, Igor Pawlak; check, Anna Kaźmierczak; formal analysis, Wiktoria Izdebska, investigation, Patrycja Sornek; resources, Agata Borkowska; data curation, Anna Kiełb; writing - rough preparation, Jakub Stanek; writing - review and editing, Radosław Ciesielski and Anna Mich. All authors have read and agreed with the published version of the manuscript.

Funding Statement
Study did not receive special funding.

Institutional Review Board Statement
Not applicable.

Informed Consent Statement
Not applicable

Acknowledgements
Not applicable.

Conflict of Interest Statement
The authors of the paper report no conflicts of interest.

Data Availability Statement
The data presented in this study are available upon request from the correspondent author.

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