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THE USE OF GOLDEN BLOOD FOR THE TREATMENT OF FETAL ERYTHROBLASTOSIS: A LITERATURE REVIEW

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ABSTRACT

Fetal erythroblastosis, also called Hemolytic Disease of the Newborn (NRHD), is a pathology that arises as a result of the incompatibility between maternal Rh-negative blood and fetal Rh-positive blood, causing the destruction of fetal red blood cells by antibodies produced by the mother. Currently, the most widespread prophylaxis consists of the administration of anti-D immunoglobulin, which aims to mitigate the risk of maternal immune sensitization to the Rh antigen. This study investigates the therapeutic potential of Rh-null blood, known as "golden blood", in the prevention of NRHD. Rh-null blood, devoid of all Rh-system antigens, represents a universal alternative for transfusions in patients with Rh incompatibility, and could theoretically serve as a basis for the development of vaccines aimed at blocking maternal sensitization to the Rh factor. An integrative literature review was performed to compare the efficacy and limitations of the use of Rh-null plasma in relation to anti-D immunoglobulin.

Keywords: Hemolytic Disease of the Newborn. Immunization. Rh null.

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INTRODUCTION

Fetal erythroblastosis, also known as hemolytic disease of the newborn, is a serious condition that occurs when there is incompatibility between the blood of the mother and the fetus, usually involving the Rh factor. This incompatibility leads to the production of maternal antibodies that cross the placenta and destroy fetal red blood cells, resulting in anemia, jaundice, and, in more severe cases, risk of life for the baby (TARELLI *et al.*, 2021).

Currently, the most used treatment for this disease is the injection of anti-D antibodies, within 72 hours after the birth of the first child, to prevent sensitization of the mother's immune system by fetal red blood cells, and consequently, the development of cells that may attack the blood factors of the next child (PASSION; OLIVEIRA, 2017).

The treatment and prevention of this condition have been improved with advances in transfusion medicine. One of the topics of growing interest in the field of hematology is the use of "golden blood", a rare blood type characterized by the total absence of Rh antigens in your red blood cells. This particularity makes it considered universal for transfusions in patients incompatible with the RH factor (FERREIRA; FIRMINO, 2022).

In this article, we will explore the therapeutic potential of golden blood in the treatment of fetal erythroblastosis, its unique properties, the difficulties related to collection and availability, as well as the ethical implications of its use in the procedure, with the aim of understanding the applicability of this blood in this treatment.

METHODOLOGY

This paper proposes an integrative literature review on the use of Rh-null blood (golden blood) for the manipulation of vaccines intended for immunization against fetal erythroblastosis and its efficacy in comparison with the anti-Rh vaccine currently used.

To carry out this review, the methodology of the study by Lopes *et al.,* (2023), was used as a reference. The following steps were followed: definition of the research question; search in scientific databases; selection of relevant studies; data extraction and analysis; presentation and discussion of the results.

Literature review will be performed to investigate immunization strategies with Rh-null blood compared to anti-Rh vaccine. Electronic databases, including Virtual Health Library (VHL) and Google Scholar, will be selected as research sources.

The search terms "Perinatal hemolytic disease," "Fetal erythroblastosis," "RH isoimmunization," "RH factor," "Rh alloimmunization," and their variations will be used, combined with Boolean operators. We found 50 studies, and 9 were chosen. Articles that were not available in Portuguese were excluded from this integrative review, since the

search was limited to publications in that language. In addition, studies published before 2009 were discarded, considering that the review was restricted to the last 15 years, in the period from 20089 to 2024. Studies focused on other hemolytic diseases unrelated to the Rh factor were also disregarded. Likewise, studies involving unrelated populations, such as those that treated autoimmune diseases with no connection to the Rh system or blood transfusions without a link to fetal erythroblastosis or as known as Perinatal Hemolytic Disease (NPHD).

RESULTS AND DISCUSSION

The results obtained are detailed in Chart 1. All articles recognize the relevance of the Rh system in medicine, especially in obstetric contexts. Understanding the molecular basis and identifying antigens are critical for the diagnosis and treatment of conditions such as erythroblastosis fetalis. The low number of articles related to the theme is due to the impossibility of robust studies with individuals with null Rh, given its low incidence in the world population.

Chart 1: Breakdown of the articles found according to the search criteria

Article	Author/Year	Goals	Results and conclusions
"Molecular bases of the Rh system and its applications in obstetrics and transfusion medicine"	NARDOZZA, et al., 2010.	Explain the molecular basis of the Rh system, including the identification of the main antigens (D, C, C, E, E) and the genetic mechanisms that determine the Rh-negative phenotype, especially in different populations. The study addresses the most common mutations, such as deletions, gene rearrangements, and insertions, and discusses the molecular differences between Caucasians and Afro-descendants regarding the absence of the D antigen, in addition to exploring the weak and partial expression of D.	The study reviews the molecular basis of the Rh system, focusing on its applications in obstetrics and transfusion medicine. The authors highlight that the Rh system is the most polymorphic and immunogenic among the blood systems, with the D antigen being the most relevant from a clinical point of view. They identify that in Caucasian individuals, complete deletion of the RHD gene is the main cause of the RhD-negative phenotype, while in Afro-descendants the RHDψ pseudogene and the RHD-CE-D hybrid gene play this role. In addition, the study points out that prophylaxis with anti-D immunoglobulin continues to be highly effective in preventing alloimmunization in RhD-negative pregnant women, although there is still a residual sensitization rate of 0.8% to 1.5%. Knowledge of molecular variations allows a better prediction of the risk of alloimmunization and can

			avoid unnecessary prophylaxis in cases of partial or weak expression of the D antigen.
"Fetal erythroblastosis: diagnosis and immunological aspects"	DA SILVA; DA SILVA; MELO. 2016.	To study fetal erythroblastosis, focusing on possible diagnoses and immunological aspects. The text highlights the importance of proper follow-up of pregnant women and timely administration of immunoglobulin to prevent the disease, which is caused by the incompatibility between the Rh+ and Rh- factors. The article also highlights the serious complications that can occur as a result of the disease, such as generalized edema, severe anemia, jaundice, cerebral palsy, and even fetal or neonatal death. in addition to providing subsidies for future studies and clarification about the disease.	The study addresses fetal erythroblastosis, highlighting the importance of early diagnosis and adequate follow-up of Rh-negative pregnant women. Diagnosis involves techniques such as the Coombs test, flowmetry, and cordocentesis. Anti-D immunoglobulin prophylaxis is effective in preventing maternal sensitization, especially if given within 72 hours of delivery. The article highlights the need for greater awareness of prevention and the importance of adequate prenatal care to reduce serious complications such as severe anemia and kernicterus. It is concluded that the lack of adequate follow-up and the late administration of immunoglobulin are still challenges in the management of the disease.
"The Efficacy of Using Human Anti-D Antiglobulin Serum in the Prevention of Fetal Erythroblastosis "	PASSION; OLIVE TREE. 2017.	To evaluate, through an integrative literature review, the efficacy and results of the use of anti-D human antiglobulin serum in the prevention of fetal erythroblastosis. The	The article discusses the efficacy of human anti-D antiglobulin serum in the prevention of fetal erythroblastosis. Prophylaxis with anti-D immunoglobulin has been shown to be effective in preventing

		search was carried out in databases such as Lilacs, SciELO and Medline, using descriptors related to the disease and treatment with anti-Rho(D) immunoglobulin. The article recommends testing the parents' Rh factor during the first pregnancy to assess the need for administration of anti-Rho(D) immunoglobulin, which reaches its peak efficacy in 2 to 3 days after application. It is concluded that, although the efficacy in partial Rho(D) individuals is not fully determined, these patients should still be considered candidates for preventive treatment with immunoglobulin.	maternal sensitization in Rh-negative pregnant women, especially when administered within 72 hours of delivery. The study underscores the importance of early diagnosis and preventive administration of serum during pregnancy, with a recommendation for application at 28 weeks and again after delivery, if necessary. Although the use of the serum is highly effective, the authors note that cases of sensitization due to inadequate follow-up or late administration still occur.
"Fetal erythroblastosis: an update of the literature"	TARELLI, *et al.*, 2021.	To review the literature on the etiology of fetal erythroblastosis, which occurs due to the destruction of red blood cells from the Rh-positive fetus by antibodies from the Rh-negative mother, with emphasis on the diagnosis and prevention of the disease. The review seeks to understand the mechanisms that trigger blood incompatibility and to evaluate strategies to identify the condition early and prevent its complications, mainly through the use of anti-Rh immunoglobulin.	The article reviews advances in the understanding and treatment of erythroblastosis fetalis, with an emphasis on the prevention of alloimmunization in Rh-negative pregnant women. The authors point out that the D antigen is the main one involved in the disease, leading to the destruction of fetal red blood cells. Early diagnosis, through tests such as indirect Coombs and ultrasounds, is essential to detect sensitization and predict the severity of fetal anemia. Treatment with exchange transfusion still plays an important role in severe cases, removing anti-Rh antibodies and correcting anemia. However, the authors conclude that anti-D immunoglobulin prophylaxis, administered within 72 hours of delivery, remains the most effective intervention to prevent maternal sensitization and protect future pregnancies. Prevention is highlighted as the best method to reduce mortality and morbidity

			related to fetal erythroblastosis.
"Fetal erythroblastosis: Role of the SUS"	DOS SANTOS; OF JESUS PEREIRA; BY AZEVEDO VILLARINHO. 2021.	To review the literature on perinatal hemolytic disease (PNHD), highlighting its relevance in terms of public health. The study addresses NPHD, caused by the incompatibility of the Rh factor, which can range from mild hemolysis to severe anemia, with complications such as hepatomegaly and splenomegaly. It also discusses treatment, including exchange transfusion and phototherapy, to prevent Kernicterus syndrome, characterized by bilirubin deposition in the brain nuclei. The article highlights the importance of adequate prenatal care and public health policies promoted by the SUS for the prevention of NPHD, in addition to pointing out the lack of data on the subject in Brazil and the need for greater awareness among pregnant women.	The study reviews the literature on Perinatal Hemolytic Disease (NPD), emphasizing its impact on public health. NPHD caused by Rh factor incompatibility can range from mild hemolysis to severe anemia, with a risk of complications such as Kernicterus. The article highlights the importance of early diagnosis and prophylaxis with exchange transfusion and phototherapy. The SUS plays a crucial role in prevention and care for pregnant women, promoting access to information and adequate prenatal care. There is still a lack of data on the subject in Brazil, and it is necessary to intensify awareness programs.
"Guide to the National Registry of Rare Blood"	FERREIRA; FIRMINO. 2022.	Present the genotypes of each rare blood type, including Rh null blood.	The guide highlights the importance of identifying and preserving rare blood donors in Brazil, with a focus on Rh-null blood. The national registry facilitates the search for donors in cases of critical transfusion need. The paper concludes that while rare blood such as Rh-null has great therapeutic potential, its scarcity poses a significant challenge. The guide reinforces the need for strategies to expand the registry and improve accessibility to rare blood in emergency situations.
"Hemolytic disease of the newborn (erythroblastosis fetalis): from	DA PAZ SILVA FILHO, *et al.*, 2022	To review the literature on the etiology, diagnosis, and treatment of Hemolytic Disease of the Newborn	The article highlights the importance of early diagnosis, with emphasis on indirect Coombs test and Doppler ultrasonography to

diagnosis to treatment"		(NRHD), highlighting the advances in diagnostic and therapeutic practices over the years and their implications for the prognosis of patients.	assess the degree of fetal anemia. Treatment techniques include intrauterine transfusions for severe fetal anemia and postnatal exchange transfusion, as well as phototherapy to treat hyperbilirubinemia. The study concludes that, despite improvements in disease management, erythroblastosis fetalis still poses a significant risk of neonatal death and neurological sequelae. Public policies for prenatal education and training of health professionals are recommended to reduce the incidence of the disease.
"Integration of blood groups and the iris"	DAYS, 2024	Explore the relationship between blood groups and iridology, associating Peter D'Adamo's findings on the blood type-based diet with iris analysis to identify health conditions. The work seeks to integrate these two approaches to improve the understanding of how blood groups influence health and well-being.	The book is based on Dr. Peter D'Adamo's studies on the influences of blood type in the development of an adequate diet to avoid various eye pathologies. For the elaboration of these treatments, this bibliography presents a detailed study on the blood types of the ABO group and the Rh group, including information on golden blood/Rh null blood (number of carriers, time of first registration). element.

Source: Author himself, 2024.

Studies such as Da Silva (2016), Tarelli (2021), and Dos Santos (2021) address fetal erythroblastosis, highlighting its etiology, diagnosis, and prevention. The need for adequate follow-up of pregnant women and the use of anti-D immunoglobulin are emphasized as effective preventive measures.

The study by Dos Santos (2021) highlights the importance of public health policies, especially in the context of the SUS, for the prevention of perinatal hemolytic disease, in line with the recommendations on adequate prenatal care.

While Nardozza (2010) focuses on the molecular basis of the Rh system and its genetic variations among different populations, other articles focus more on the clinical implications of erythroblastosis fetalis and the effectiveness of preventive interventions. Paixão (2017) discusses the efficacy of anti-D immunoglobulin in individuals with partial Rh, suggesting that its efficacy is not fully determined. In contrast, other studies affirm the importance of preventive treatment without discussing specific limitations.

Erythroblastosis fetalis or Hemolytic Disease of the Newborn (DHRN) is an alteration that occurs in blood incompatibility between the mother, who has the Rh negative factor (Rh-), and the baby, who is Rh positive (Rh+). This condition causes Rh antibodies to be produced in response to erythrocyte alloimmunization after blood transfusion and/or pregnancy (DA PAIXÃO; OLIVEIRA, 2017).

In this way, the mother's body, when having contact with the Rh + of the perinate during labor, produces antibodies that will fight the red blood cells of the baby from a second pregnancy. This alteration can also appear, in a blood transfusion, if the mother receives Rh + blood, sensitizing the immune system. It is estimated that 97% of cases of erythroblastosis fetalis are caused by maternal anti-Rho(D) antibodies, and that this condition is present in 6% of all births (DA PAIXÃO; OLIVEIRA, 2017).

Thus, pregnant women should have their blood typing and the existence of anti-D immunoglobulin tested early. The presence or absence of antibodies must be verified, while blood typing must also include paternal blood, in order to classify the possible fetal blood group. With this data, the physician is able to estimate the risk of fetal erythroblastosis, in addition to guiding the appropriate procedures for the administration of the serum and monitoring of intrauterine fetal tissue lesions (PASSION; OLIVEIRA, 2017).

This disease, in its most severe cases, affects the baby's liver, causing parenchymal distension, liver failure, hypoalbuminemia and fetal hydropesia. In addition, the accumulation of bilirubin, after birth, can trigger jaundice and even Kernicterus (OF PASSION; OLIVEIRA, 2017).

The most used alternative for the prevention of fetal erythroblastosis is the administration of Anti-D serum to the pregnant woman after the first delivery, or before the first delivery when there is already a record of contact with Rh positive blood. This serum, composed of antibodies against the D antigen, attacks fetal blood cells that had contact with maternal blood during the first birth. (DOS SANTOS; OF JESUS PEREIRA; BY AZEVEDO VILLARINHO, 2021.)

Thus, for Rh- pregnant women, there is the advent of anti-D immunoglobulin, to be administered to the mother in the 28th week of gestation and up to 72 hours after the delivery of the first child, with the purpose of preventing the formation of memory cells by the maternal immune system. In this way, if the next children are also Rh positive, there will be no risk of the immune system compromising fetal blood cells. This preventive intervention is extremely effective and has a significant limitation to the influence of hemolytic disease in the newborn in recent decades (DA PAIXÃO; OLIVEIRA, 2017).

Rh-null blood, often referred to as "golden blood," is one of the rarest variants of blood types ever documented, with fewer than 45 people worldwide identified with this condition since its discovery in 1961. This blood type is characterized by the complete absence of all 61 antigens of the Rh system, which makes it unique (DIAS, 2024).

The "D" negative phenotype (D-) is characterized by the absence of the RhCE protein in the erythrocyte membrane, due to mutations in the RHCE gene or to gene rearrangements between RHD and RHCE. Consequently, D- individuals have the rare phenotype RH:1,-2,-3,-4,-5, marked by the marked expression of the RH1 antigen (due to the presence of the RHD gene in homozygosis) and the absence of the other RhCE antigens (FERREIRA *et al.,* 2022).

Thus, this blood type, given the lack of the Rh factor, is an alternative for the prevention of NRHD and works like a serum. This blood, rich in immunoglobulins against Rh factors, when administered to a pregnant woman compatible with the possibility of erythroblastosis - that is, maternal blood Rh- and fetal blood Rh+ -, prevents isoimmunization through fetal blood of the firstborn, and consequently, immune attack on the second child Rh+. For this reason, Rh-null blood is considered universal for doing actions to individuals with Rh-negative blood types, so it is especially useful in the treatment of erythroblastosis (NARDOZZA *et al.,* 2010).

However, the biggest challenge is the handling of Rh-null blood, given the rarity of this blood type. Because donors are virtually nonexistent, patients often need to maintain their own blood stocks in case of emergencies, which makes access to blood very limited and time-consuming. The characteristic that determines it unique and efficient in the evolution of DHRN prevention is the same that compromises the feasibility of its application in the medical setting: its rarity (DA PAZ SILVA FILHO *et al.,* 2022).

CONCLUSION

The findings of the review indicate that the use of Rh-null blood-derived antigens may represent a promising alternative to prevent maternal sensitization to the Rh factor. The absence of antigens in Rh-null blood would allow the development of vaccines that act by blocking the immune response against the D antigen, thus reducing the risk of fetal erythroblastosis in subsequent pregnancies. However, the practical applicability of this approach is still limited by the scarcity of clinical studies demonstrating its efficacy and safety in Rh-negative pregnant women.

Thus, while immunization with Rh-null plasma could, in theory, prevent maternal sensitization more efficiently, its practical use still encounters significant obstacles and requires further clinical studies to evaluate its safety and efficacy.

The results suggest that the application of Rh-null blood for immunization, although feasible in an experimental context, is not yet presented as a practical solution to replace anti-D immunoglobulin in the prevention of fetal erythroblastosis. Thus, anti-D immunoglobulin remains the most advantageous and accessible intervention in current clinical management.

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