GOIANA JOURNAL OF MEDICINE

DOI 10.63162/V67N70E26712
ISSN 0034-9585
e26712
SCIENTIFIC ARTICLE - CASE REPORT

INTRAUTERINE BLOOD TRANSFUSION IN SEVERE PERINATAL HEMOLYTIC DISEASE: A CASE REPORT

ARTHUR AUAD OLIVEIRA[1], LUÍS GUSTAVO AUAD OLIVEIRA[2], LUÍS AUGUSTO VICENTINI[1], BEATRIZ ARAÚJO VENCIO[3], KAMILA DE OLIVEIRA GONÇALVES SOUZA[4], WALDEMAR NAVES DO AMARAL[5]

1. Graduando no Centro Universitário de Mineiros - UNIFIMES, Tindade/GO, Brazil.
2. Graduando na Faculdade de medicina ZARNS, Itumbiara/GO, Brazil.
3. Pontifícia Universidade Católica de Goiás - PUC, Goiânia/GO, Brazil.
4. Schola Fertile Treinamentos em Medicina, Goiânia/GO, Brazil.
5. Professor do Departamento de Ginecologia e Obstetrícia e diretor da Faculdade de Medicina - UFG/GO, Goiânia/GO, Brazil.

ABSTRACT

The objective of this work is to describe and analyze the clinical management of a pregnant woman with perinatal hemolytic disease (PHD) undergoing intrauterine blood transfusion (IUT), with emphasis on the main diagnostic, therapeutic, and prognostic points involved in the case. The specific objectives are: to present the main aspects of perinatal hemolytic disease; to describe the diagnostic processes of the disease; and to analyze intrauterine blood transfusion in patients with perinatal hemolytic disease. The severity of the case is related to the high titer of maternal anti-Rh fetal antibodies (titration: 1/2048) and the number of transfusions, which was far above the usual average (9 transfusions).

Keywords: Anti-d antibodies, Perinatal hemolytic disease, RH factor, Pregnancy, Intrauterine transfusion.

INTRODUCTION

Perinatal hemolytic disease (PHD) is one of the most relevant immunological complications associated with pregnancy, characterized by the destruction of fetal red blood cells mediated by maternal antibodies capable of crossing the placental barrier. It is a potentially severe condition that may result in progressive fetal anemia, heart failure, fetal hydrops, and intrauterine death, especially when not diagnosed or treated in a timely manner.[1]

Historically, PHD has been strongly associated with incompatibility of the Rh system, particularly related to the D antigen. Before the introduction of anti-D immunoglobulin prophylaxis, this condition was responsible for high rates of perinatal morbidity and mortality. Despite advances in prevention, the disease persists as a public health problem, particularly in countries with limited access to adequate prenatal care or failures in the implementation of preventive strategies.[2]

In cases of maternal sensitization, the IgG antibodies produced recognize fetal erythrocyte antigens as foreign, triggering a process of chronic hemolysis. This erythrocyte destruction compromises fetal oxygenation, leading to cardiovascular adaptations that, when exceeding the fetus's compensatory capacity, result in severe conditions such as fetal hydrops.[3]

In this context, intrauterine blood transfusion (IUT) has been established as one of the most important

therapeutic interventions in the management of severe fetal anemia secondary to PHD. The procedure consists of the direct infusion of packed red blood cells into the fetal circulation, allowing rapid correction of anemia, improvement of tissue oxygenation, and significant reduction in intrauterine mortality rates.[4]

The main objective of this study is to describe and analyze the clinical management of a pregnant woman with perinatal hemolytic disease (PHD) who underwent intrauterine blood transfusion (IUT), with emphasis on the main diagnostic, therapeutic, and prognostic aspects involved in the case. The specific objectives are: to present the main aspects of perinatal hemolytic disease; to describe the diagnostic processes of the disease; and to analyze intrauterine blood transfusion in patients with perinatal hemolytic disease.

Severity was based on the anti-Rh antibody titer (1:2048) and the high number of transfusions.

LITERATURE REVIEW

Perinatal Hemolytic Disease

Perinatal hemolytic disease (PHD) is defined as an immunological condition resulting from incompatibility between antigens present on fetal red blood cells and specific maternal antibodies, leading to the destruction of these blood cells either during intrauterine life or in the early neonatal period. This incompatibility occurs predominantly when the mother is previously sensitized to erythrocyte antigens inherited by the fetus from the father.[2]

The main characteristic of PHD is the progressive hemolysis of fetal red blood cells mediated by IgG immunoglobulins, which are capable of crossing the placenta. The severity of the disease varies according to the type and titer of maternal antibodies, as well as the fetus's compensatory capacity, and may range from mild forms to severe cases with systemic involvement.[5]

Clinically, PHD may manifest as fetal anemia, neonatal hyperbilirubinemia, jaundice, hepatosplenomegaly, and, in more severe cases, fetal hydrops. The severity of the condition is directly related to the rate of erythrocyte destruction and gestational maturity, with early diagnosis being a determining factor for therapeutic success.[6]

Rh incompatibility, particularly related to the D antigen, is considered the main classical cause of perinatal hemolytic disease. This condition occurs when an Rh-negative pregnant woman is exposed to Rh-positive fetal red blood cells, usually during delivery, miscarriage, invasive procedures, or episodes of transplacental bleeding, leading to maternal immunological sensitization.[1]

After sensitization, the mother begins to produce anti-D antibodies which, in subsequent pregnancies with Rh-positive fetuses, cross the placenta and promote the destruction of fetal red blood cells. The intensity of the immune response may increase progressively with each exposure, raising the risk of severe forms of the disease.[7]

Despite the widespread use of anti-D immunoglobulin prophylaxis having significantly reduced the incidence of PHD due to Rh incompatibility, this etiology is still observed in contexts of prophylaxis failure, late diagnosis, or lack of adequate prenatal care.[5]

Diagnosis of Hemolytic Disease

Maternal diagnosis of perinatal hemolytic disease is an essential step in the prevention, early identification, and appropriate management of the condition. Systematic evaluation during prenatal care allows the identification of pregnant women at risk of alloimmunization and the implementation of timely preventive or therapeutic measures.[1]

Early identification of maternal blood group and Rh factor is considered one of the main strategies for preventing perinatal hemolytic disease. Blood typing should preferably be performed at the first prenatal visit, enabling the identification of Rh-negative pregnant women at potential risk of sensitization.[6]

In Rh-negative pregnant women, determination of the paternal Rh factor and careful monitoring throughout pregnancy are fundamental for the prevention of alloimmunization. Prophylactic administration of anti-D immunoglobulin, when indicated, has significantly reduced the incidence of perinatal hemolytic disease associated with the Rh system.[7]

Despite advances in prophylaxis, failure to identify the Rh factor early or lack of adequate follow-up remain factors associated with the occurrence of severe cases of the disease, particularly in settings with inadequate prenatal care.

Screening for irregular antibodies, performed using the indirect Coombs test, is essential for detecting maternal antibodies capable of causing fetal hemolysis. This test allows not only the identification of antibodies but also their titration, assisting in the assessment of fetal risk.[2]

Serial antibody titration is used to monitor the progression of alloimmunization throughout pregnancy. High or rising titers are associated with a greater risk of severe fetal anemia, although the correlation between titer and severity is not absolute, especially in cases involving antibodies of the Kell system. Pregnant women with a history of moderate or severe perinatal hemolytic disease and initial anti-D antibody titers equal to or greater than 1:128 have a 3.3-fold higher risk of requiring intrauterine transfusion or progressing to fetal death during prenatal follow-up. On the other hand, the presence of anti-D antibodies associated with other anti-erythrocyte antibodies did not show a significant relationship with the evaluated outcomes.[7]

Early detection of irregular antibodies allows referral of the pregnant woman to specialized fetal medicine centers, where appropriate follow-up can be performed and therapeutic interventions instituted when necessary.[6]

Obstetric ultrasonography is a fundamental tool in fetal evaluation, allowing the identification of indirect signs of anemia. Among the most relevant findings are cardiomegaly, hepatosplenomegaly, and the presence of fetal hydrops, which indicate hemodynamic decompensation. Hepatosplenomegaly reflects increased extramedullary erythropoiesis, while cardiomegaly indicates cardiac overload secondary to anemia. The identification of these ultrasonographic findings reinforces the need for detailed investigation and close monitoring.[6] The presence of fetal hydrops is a marker of severity and is associated with a worse prognosis, requiring immediate intervention to reduce the risk of intrauterine death.

Doppler ultrasound of the middle cerebral artery (MCA) is considered the main noninvasive method for screening fetal anemia, especially in high-risk pregnancies, such as those involving Rh alloimmunization. This examination evaluates the peak systolic velocity of blood flow in the MCA, which is increased in anemic fetuses due to reduced blood viscosity. Peak systolic velocity values greater than 1.5 multiples of the median (MoM) are associated with a high probability of moderate to severe fetal anemia. The use of this method has the significant advantage of reducing the need for invasive procedures, such as cordocentesis, in approximately 50% to 70% of cases, thereby decreasing fetal risks. MCA Doppler is generally performed every one to two weeks, starting from the 16th to 18th week of gestation.[6]

Intrauterine Blood Transfusion

Intrauterine blood transfusion (IUT) is defined as an invasive fetal medicine procedure that consists of the infusion of packed red blood cells directly into the fetal circulation, with the main objective of

correcting severe fetal anemia. This intervention aims to restore oxygen-carrying capacity, reduce tissue hypoxemia, and prevent progression to heart failure and fetal hydrops.[8]

In the context of perinatal hemolytic disease, IUT represents the main therapeutic modality capable of interrupting the cycle of progressive hemolysis. By increasing fetal hemoglobin levels, the procedure promotes immediate improvement in systemic oxygenation and hemodynamic stabilization, allowing the continuation of pregnancy to safer gestational ages for delivery.[9]

The procedure is performed under strict ultrasound guidance, ensuring continuous visualization of fetal structures and the puncture site. The most commonly used approach today is the intravascular route, with access to the umbilical vein, considered the safest and most effective technique. This approach allows rapid correction of anemia and direct monitoring of the fetal response to treatment.[3]

IUT is primarily indicated in cases of moderate to severe fetal anemia, diagnosed by noninvasive or invasive methods, and should be performed in specialized centers with a multidisciplinary team experienced in invasive fetal medicine. Despite its invasive nature, when properly indicated and performed, it has a high success rate and a positive impact on perinatal outcomes.[4]

The historical evolution of intrauterine blood transfusion reflects technological and scientific advances in fetal medicine. The first attempts to treat fetal anemia occurred in the 1960s, when transfusion was performed via the intraperitoneal route, a pioneering technique that consisted of infusing blood into the fetal abdomen, allowing gradual absorption through the lymphatic system.[9]

Although innovative for its time, the intraperitoneal approach had significant limitations, such as unpredictable absorption of the transfused volume, delayed therapeutic response, and a higher risk of failure in cases of fetal hydrops. These limitations led to the development of more precise and effective techniques, culminating in the introduction of intravascular intrauterine transfusion.[3]

With improvements in real-time ultrasonography and Doppler velocimetry, direct access to the fetal circulation became possible, particularly to the umbilical vein near the placental insertion. This approach enabled greater procedural control, immediate correction of anemia, and a significant reduction in complications associated with the technique.[4]

Currently, intravascular intrauterine blood transfusion is considered the gold standard for the treatment of severe fetal anemia. Technical advancements have played a decisive role in reducing fetal mortality associated with perinatal hemolytic disease, transforming the management of this condition and expanding the possibilities for survival and favorable neonatal outcomes.

CASE REPORT

Patient D.A., 31 years old, blood type O negative, G3P3N1C2A0. The first child was born with blood type O positive, and the second A positive. All children are from the same partner, who is A positive. At the beginning of the third pregnancy, the patient presented with transvaginal bleeding, and ultrasound identified a small placental abruption, for which Utrogestan 200 mg and relative rest were prescribed.

She had not received human immunoglobulin in previous pregnancies; however, the indirect Coombs test (ICT) was negative at that time. At 20 weeks of gestation, the patient presented an ICT titer of 1:2048. A morphological ultrasound was performed at 22 weeks, and Doppler of the middle cerebral artery (MCA) was abnormal, indicating a positive screening for fetal anemia. Subsequently, a diagnostic cordocentesis was performed, identifying fetal blood group O positive, positive direct Coombs test, and fetal anemia based on hematocrit and hemoglobin levels. At 24 weeks, intrauterine blood transfusions

were initiated under ultrasound guidance and local anesthesia, totaling nine transfusions, performed via the intraperitoneal route, with volumes ranging from 70 mL to 95 mL of O-negative blood.

At 25 weeks of gestation, another cordocentesis was performed with the collection of 3 mL of fetal blood, without complications. Fetal blood typing at this evaluation confirmed O positive. Fetal Doppler ultrasound performed at 28 weeks showed no abnormalities. Additional Doppler ultrasounds were performed, all demonstrating normal flow, normal hemodynamic profile, and normal myocardial function.

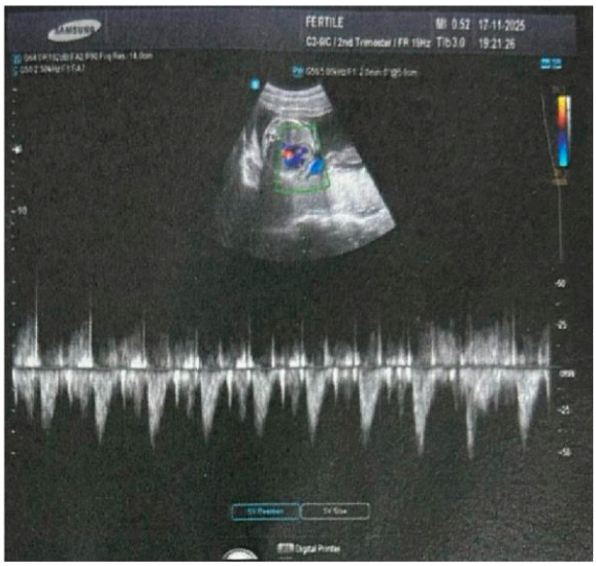

Figure 1: Obstetric ultrasound with Doppler at 23 weeks.

The patient received corticosteroid therapy for fetal lung maturation, and a cesarean section was performed at 34 weeks and 6 days of gestation. The newborn was delivered weighing 2070 g, with an Apgar score of 8/9. Umbilical cord blood analysis showed a negative direct Coombs test and blood type O negative, a result likely influenced by the intrauterine transfusions.

The newborn was admitted to the Intensive Care Unit (ICU) due to respiratory distress. On physical examination, the infant presented with a distended abdomen, soft and non-tender on palpation, liver palpable 2.0 cm below the costal margin, palpable splenic tip, and present bowel sounds. There was no evidence of hydrops or edema. Single and double phototherapy were initiated. Laboratory findings showed: red blood cells 6.4×10^{12}/L, hemoglobin 19.0 g/dL, hematocrit 51.1%, total leukocytes 5,730/µL, total bilirubin 10.60 mg/dL, direct bilirubin 0.71 mg/dL, and indirect bilirubin 9.89 mg/dL. The newborn evolved with elevated hemoglobin and moderate indirect hyperbilirubinemia, without indications for exchange transfusion or human immunoglobulin therapy. Transfontanelle ultrasound was normal, as was the upper abdominal ultrasound. The fetal echocardiogram revealed a small ostium secundum atrial septal defect (ASD) measuring 3.5 mm. After 10 days, repeat laboratory tests demonstrated favorable clinical evolution: hemoglobin 15.1 g/dL, hematocrit 42.4%, total bilirubin 3.50 mg/dL, direct bilirubin 0.66 mg/dL, and indirect bilirubin 2.84 mg/dL. The newborn was discharged nineteen days later in good general condition.

Figure 2: Newborn in the incubator.

DISCUSSION

Perinatal hemolytic disease (PHD) remains a highly relevant condition in obstetric practice, even with the consolidation of anti-D immunoprophylaxis. The introduction of anti-Rh immunoglobulin in the 1960s marked a significant turning point in the control of maternal isoimmunization, substantially reducing the occurrence of the most severe forms of the disease (Nardozza, 2020). Studies indicate that, when correctly administered in the postpartum period and in risk situations such as miscarriages and invasive procedures, prophylaxis can reduce maternal sensitization by up to 85–90% of cases.[7]

In the case described, the absence of immunoprophylaxis in previous pregnancies was the main factor leading to the development of maternal alloimmunization. The patient reached the 20th week of gestation with an indirect Coombs titer of 1:2048, an extremely high value directly associated with a high risk of severe fetal anemia.

Dantas et al.[7] report that titers equal to or greater than 1:128 are associated with a substantially increased risk of requiring intrauterine transfusion or resulting in fetal death. Therefore, the patient's clinical condition required intensive follow-up in a specialized referral center.

Doppler velocimetry of the middle cerebral artery (MCA) has been established as a valuable noninvasive tool for screening fetal anemia in the context of PHD. When peak systolic velocity exceeds 1.5 multiples of the median (MoM), there is high sensitivity for detecting moderate to severe anemia, allowing unnecessary invasive procedures to be avoided.[6] In the present case, serial Doppler assessments demonstrated maintenance of the fetal hemodynamic profile after each transfusion, confirming a satisfactory therapeutic response and clinical stability.

Intrauterine blood transfusion (IUT) is recognized as the gold standard treatment for severe fetal anemia associated with Rh alloimmunization.[8] The procedure promotes immediate recovery of fetal hemoglobin levels, improvement in oxygenation, and prevention of progression to hydrops. Arnold et al.[4] emphasize that, when performed by a trained team in a specialized center, IUT has a high success rate and a direct impact on perinatal survival.

In this report, nine intrauterine transfusions were performed via the intraperitoneal route. Although

the intravascular route is currently the preferred approach in most centers, the intraperitoneal technique remains a clinically appropriate alternative in specific scenarios, particularly when fetal vascular access is unfavorable.[3] The absence of fetal hydrops and the preservation of myocardial function throughout follow-up demonstrate the effectiveness of the treatment and the progressive control of anemia.

Delivery occurred at 34 weeks and 6 days, preceded by corticosteroid therapy for fetal lung maturation—a measure widely recommended to reduce respiratory morbidity in preterm neonates.[9] The newborn presented with elevated hemoglobin levels and moderate indirect hyperbilirubinemia, without indication for exchange transfusion.

The negative direct Coombs test and identification of blood type O negative in the neonate are likely attributable to the cumulative effect of intrauterine transfusions, with partial replacement of the fetal erythrocyte pool by donor red blood cells, a phenomenon widely documented in the literature.[4]

The favorable neonatal outcome reinforces the central importance of early diagnosis, continuous monitoring, and timely intervention in the management of PHD. Cunha et al.[5] highlight that the integrated work of obstetricians, hematologists, neonatologists, and nursing staff is crucial for achieving better perinatal outcomes.

However, despite notable technical and scientific advances, significant structural challenges persist in Brazil, particularly regarding equitable access to anti-D immunoglobulin and the quality of prenatal care across different regions. National scientific literature demonstrates that gaps in prevention still account for a substantial proportion of severe PHD cases.[2]

CONCLUSION

The present study reinforces the data available in the literature by demonstrating that intrauterine transfusion, when indicated based on appropriate clinical criteria and performed in an adequate setting, is a safe and effective procedure capable of significantly improving fetal prognosis. The case also highlights the urgency of strengthening preventive policies, expanding access to immunoprophylaxis, and investing in the continuous training of healthcare teams in order to reduce the incidence and severity of perinatal hemolytic disease throughout the country.

REFERENCES

1. Araujo CSR, Machado BA, Palaoro JS, Guadagnin MF, Azerebo SB, Rech JL, Pian LCM, Rossato V, Pasqualotti A, Castilho LM. Alerta para a importância da abordagemmultiprofissional na doença hemolítica perinatal: um relato de caso. Hematol Transfus Cell Ther. 2023 Oct;45(Suppl 4):S764–S765.

2. Nardozza LMM. Doença hemolítica perinatal. Femina. 2020;48(6):369–374.

3. Memare KC, Picelli SM, Cossolino GL, Castro AB, Jamas MT, Miranda CL, Garcia PC .Aloimunização em gestantes e o desfecho terapêutico neonatal na doença hemolítica do feto e recém-nascido (DNFRN). Hematol Transfus Cell Ther. 2022;44(Suppl 2):S445.

4. Arnold BB, Souza MT, Menezes LP, Cal BB, Castro AB, Miranda CL, Bonichini-Junior P,Marcondes TS, Almeida LL, Garcia-Bonichini PC. Doação materna de sangue raro para exsanguineotransfusão em recém-nascido com doença hemolítica. Hematol Transfus Cell Ther. 2023 Oct;45(Suppl 4):S755–S756.

5. Cunha TAA, Santos JCC, Santanna AN, Cruz VV. A importância das orientações doenfermeiro para gestante com doença hemolítica perinatal: revisão integrativa. Res Soc Dev. 2020 Jul;9(8):e669986184.

6. Ferreira KSS. Morbimortalidade por doença hemolítica do feto e do recém-nascido entre2009 e 2019 no estado do Maranhão. Rev Multidiscip Saude. 2021;2(1):23.

7. Dantas ILS, Paiva LBS, Silva APBP, Teles WS, Silva MC, Oliveria FKF, Andrade ANM, Oliveira SS, Andrade MN. Doença hemolítica do feto e do recém-nascidopor aloimunização Rh: uma revisão de literatura. Res Soc Dev. 2024 Jul;13(7):e3213746248.

8. Gambarra BF, Espínola PFLA, Silva HBSLG, Botelho LFB, Sousa DR, Braga EPC. Análise hematológica da transfusão intrauterina no tratamento da anemia fetal: uma revisão sistemática. Hematol Transfus Cell Ther. 2020 Nov;42(Suppl2):381.

9. Alves ST, Moraes CDV, Fernandes SR, Oliveira JSR. Manejo hemoterápico de pacientesubmetida a transfusão intrauterina: relato de caso. Hematol Transfus Cell Ther. 2021 Oct;43(Suppl 1):S398–S399.

MAILING ADDRESS

ARTHUR AUAD OLIVEIRA
Rua A20, Bairro Jardins Atenas, Goiânia/GO, Brazil.
E-mail: arthurauadoliver@gmail.com

EDITORIAL AND REVIEW

Authors:
Arthur Auad Oliveira - http://lattes.cnpq.br/5472122384487937 - https://orcid.org/0009-0008-7126-2987

Luís Gustavo Auad Oliveira - http://lattes.cnpq.br/8004382619599123 - https://orcid.org/0009-0003-8947-8480

Luís Augusto Vicentini - http://lattes.cnpq.br/8030401312705442 - https://orcid.org/0009-0009-9478-6019

Beatriz Araújo Vencio - http://lattes.cnpq.br/0664983927270492 - https://orcid.org/0009-0006-4338-283X

Kamila De Oliveira Gonçalves Souza - http://lattes.cnpq.br/0042950644624611 - https://orcid.org/0000-0003-1525-6298

Waldemar Naves do Amaral - http://lattes.cnpq.br/4092560599116579 - https://orcid.org/0000-0002-0824-1138

Library Review: Izabella Goulart
Spell Check: Dario Alvares
Translation: Soledad Montalbetti
Received: 22/03/26. Accepted: 22/03/26. Published in: 06/05/2026.