

Management of Three Cases of Hemolytic Disease of the Fetus and Newborn Due to Anti-Rh17 Alloimmunization Within the Same Family by a Rural Hospital Blood Bank

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Hemolytic disease of the fetus and newborn (HDFN) due to anti-Rh17 alloimmunization is rare, with very few cases reported among siblings in the same family. This case series describes three biological sisters, all with blood type O and RhCE-null phenotype (genotype D⁻/D⁻), who were evaluated over a three-year period. Two of the sisters developed anti-Rh17 antibodies due to pregnancy, resulting in three separate cases of HDFN in their newborns. The pregnancies were managed collaboratively by a rural hospital blood bank, a tertiary care hospital, and several reference laboratories. Management strategies included prenatal antibody screening, identification and titration, intrauterine interventions, and postnatal blood transfusions using antigen-compatible red blood cells to treat fetal anemia and hyperbilirubinemia. Despite limited resources in the rural setting, coordinated multidisciplinary care enabled the successful management of these complex cases. This report highlights the critical role of early detection, the availability of rare blood units, and the value of collaboration across healthcare systems. It also emphasizes the importance of specialized knowledge in transfusion medicine for managing rare maternal antibodies like anti-Rh17 to improve neonatal outcomes.

Abbreviations: AC, autocontrol; ARC, American Red Cross; DAT, direct antiglobulin test; HDFN, hemolytic disease of the fetus and newborn; IRL, Immunohematology Reference Laboratory; IUFD, intrauterine fetal demise; IUT intrauterine transfusion; IVIG, intravenous immunoglobulin; MCA-PSV, middle cerebral artery peak systolic velocity; pRBCs, packed red blood cells; TPE therapeutic plasma exchange.

Keywords: Hemolytic disease of the fetus and newborn (HDFN), anti-Rh17, RhCE-null phenotype, D⁻/D⁻

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Introduction

Rh17 (Hr₀) is a high-prevalence Rh antigen found in approximately 99.9% of the population.¹ It comprises a group of epitopes located on all common RhCE proteins, except in individuals with the RhCE-null (genotype D⁻/D⁻) or Rh-null phenotypes.¹⁻⁴ Anti-Rh17 (anti-Hr₀) antibody is a single antibody with broad and complex specificity, reacting with C/c and E/e antigens.¹ Although rare, anti-Rh17 has been implicated in mild to severe hemolytic disease of the fetus and newborn (HDFN).^{1, 5-8} This review describes three cases of HDFN caused by anti-Rh17 in siblings from an American Hispanic family. The family includes three biological sisters, each spaced approximately three years apart in age. Over a three-year follow-up period, their ages ranged as follows: Sister 1 was 25-28 years old, Sister 2 was 22-25 years old, and Sister 3 was 19-22 years old.

Patient Profile

Sister 1

At 24 years of age, Sister 1 presented to the emergency department of a rural regional hospital with complaints of abdominal pain, nausea, and vomiting. Upon admission, laboratory tests and imaging studies indicated acute cholecystitis, requiring emergent cholecystectomy. During the pretransfusion workup, serologic testing revealed Sister 1's blood type as O, Rh(D) positive. Her antibody screen was positive with all red cell panels. Antibody identification showed pan-reactivity with all red cells on the antibody identification panels, while the autocontrol (AC) and direct anti-globulin test (DAT) were both negative. Cross-matching attempts failed to find any compatible units with the patient's plasma. Due to the urgency of the surgery and the complex serologic findings, Sister 1's specimen was sent to the regional American Red Cross (ARC) Immunohematology Reference Laboratory (IRL) for further antibody identification.

While awaiting results from the IRL, Rh extended phenotyping was performed for Sister 1. Her Rh phenotype was determined to

be D⁺, C⁻, c⁻, E⁻, e⁻, consistent with the rare D⁻/D⁻ genotype. Subsequent IRL testing identified the presence of anti-Rh17 antibody in her plasma and ruled out any additional underlying alloantibodies. Red blood cell antigen typing results further confirmed the RhCE-null phenotype.

Family members

Due to the rarity of the RhCE-null phenotype and the presence of anti-Rh17 antibody, an immunohematological workup was performed for Sister 1's immediate family members, including her husband, first child, father, mother, Sister 2, and Sister 3. The results are summarized in Table 1. Molecular genotyping was not performed due to health insurance limitations, which restricted access to advanced diagnostic testing. As a result, Rh genotype determination was based on serologic phenotyping and family inheritance patterns.

Table 1. Blood Typing, Rh Phenotype, and Presumed Genotype of Sister 1's Family

	Blood typing		Rh phenotyping	Presumed Rh genotype
	ABO	Rh(D)		
Sister 1	O	POS	D+ C- c- E- e-	D ⁻ /D ⁻
Husband	O	POS	D+ C+ c+ E+ e+	R1/R2
First child	O	POS	D+ C+ c+ E- e+	R1/D ⁻
<i>Parents and siblings</i>				
Father	O	POS	D+ C+ c- E- e+	R1/D ⁻
Mother	O	POS	D+ C+ c- E- e+	R1/D ⁻
Sister 2	O	POS	D+ C- c- E- e-	D ⁻ /D ⁻
Sister 3	O	POS	D+ C- c- E- e-	D ⁻ /D ⁻

ABO, blood type; POS, positive; Rh(D), RhD antigen.

Sister 1's parents were in a consanguineous marriage and were found to be compound heterozygotes for the DCe/D⁻. Sister 1 experienced an uneventful first pregnancy and delivered a healthy baby at 23 years of age in a non-consanguineous marriage, with no history of transfusion or miscarriage. Sister 1's husband was determined as DCe/DcE. Both Sister 2 and

Sister 3 - also homozygous for the D⁻/D⁻, did not have a history of pregnancy or previous transfusion.

Diagnostic Processes

Clinical interventions

Sister 1

During Sister 1's second pregnancy at 25 years of age, prenatal screening and monitoring were initiated early in the first trimester. At 12 weeks' gestation, her baseline anti-Rh17 titer was measured at 4, and the pregnancy progressed normally through the second trimester. However, a significant rise in anti-Rh17 titer was observed at 27 weeks' gestation, reaching 2048, representing an eight-fold increase, as reported by the regional reference laboratory, Quest Diagnostics. At 28 weeks' gestation, the fetus developed hydrops fetalis and experienced intrauterine fetal demise (IUFD).

Due to the limited capacity of the rural regional hospital and Sister 1's complicated obstetric history, she was referred to a tertiary hospital for management of her third pregnancy at the age of 26. Doppler ultrasonography was used to monitor for fetal anemia, specifically measuring middle cerebral artery peak systolic velocity (MCA-PSV). There were no signs of fetal anemia until the early third trimester. In preparation for delivery, Sister 1 completed a 500 mL autologous whole blood donation at gestational age of 30 weeks for potential use during her scheduled cesarean section. Additionally, Sister 2 made a directed donation of 250 mL of antigen-compatible packed red blood cells (pRBCs), which was aliquoted into small pediatric bags, each containing approximately 30 mL of pRBCs. Two aliquots were stored in the blood bank refrigerator to support potential intrauterine transfusions (IUTs) in the event fetal anemia was detected. The remaining six

aliquots were cryopreserved to ensure the availability of antigen-compatible pRBCs for the neonate, if needed in the future.

Sister 1's initial anti-Rh17 antibody titer was 8 and increased gradually, though not significantly, throughout early third trimester. However, at 32 4/7 weeks' gestation, the titer rose sharply to 2,048. Concurrently, the middle cerebral artery peak systolic velocity (MCA-PSV) exceeded 1.5 multiples of the median (MoM), indicating a high likelihood of fetal anemia. Given the elevated risk, early delivery by cesarean section was performed at 33 week's gestation as the most favorable option for both maternal and fetal outcomes. The newborn's Rh phenotype was determined to be D⁺, C⁺, c⁻, E⁻, e⁺, with a presumed genotype of DcE/D⁻, as shown in Table 2.

Table 2. Laboratory Testing and HDFN Outcomes for Sister 1 and Siblings Over Three Years

	Antibody screen & identification panel	AC & DAT	Antibody presence	HDFN & outcome
Sister 1 (25y-28y)				
1 st pregnancy (23y)	NK	NK	NK	Normal
2 nd pregnancy (25y)	All positive	Negative		IUFD
3 rd pregnancy (26y) Infant (DcE/D ⁻)	All positive	Negative		Moderate HDFN, alive
Sister 2 (22y-25y)	All negative	Negative	None	
Sister 3 (19y-21y)				
19y-20y	All negative	Negative	None	
1 st pregnancy (21y) Infant (DcE/D ⁻)	All positive	Negative	Anti-Rh17	Mild HDFN, alive

AC, autocontrol; Anti-Rh17, anti-Rh17 antibody; DAT, direct antiglobulin test; HDFN, hemolytic disease of the fetus and newborn; IUFD, intrauterine fetal demise; NK, not known.

The infant developed moderate hyperbilirubinemia and anemia, requiring intravenous immunoglobulin (IVIG) infusions, phototherapies, an exchange transfusion and antigen-compatible pRBCs transfusion, directly

donated by Sister 2. One week after discharge from the tertiary hospital, the infant received an additional 50 mL transfusion of rejuvenated, deglycerolized, and irradiated antigen-compatible pRBCs at the local rural hospital. This unit was prepared and shipped from the tertiary hospital via the ARC transport service. Three days later, the baby was discharged with stable condition from the local hospital.

Sister 3

Sister 3 had no history of pregnancy or blood transfusion and consistently tested negative for red cell antibodies during the first two years of the observation period. She made a directed donation of pRBCs and cryopreserved prior to pregnancy for potential future use. Her first pregnancy occurred at age 21, and the antenatal course was unremarkable. She delivered at 38 weeks of gestation. Upon delivery, Sister 3's antibody screen was positive, and the antibody was identified as anti-Rh17 with a titer of 16. No additional alloantibodies were detected, as reported by the ARC IRL. The newborn's cord blood was DAT-positive, and the baby presented with mild anemia and hyperbilirubinemia. Anti-Rh17 was also identified in the eluate from the cord blood. The infant's Rh phenotype was D+, C-, c+, E+, e-, with a presumed DcE/D--, as shown in Table 2. An immediate transfusion of 30 mL of antigen-compatible, rejuvenated, deglycerolized and irradiated pRBCs, previously donated by the mother, was administered, followed by phototherapy. The baby was discharged one week later in stable condition, with no further pRBCs transfusions required.

Sister 2

Sister 2 had no history of pregnancy or transfusion and consistently maintained a negative antibody screen throughout the three-year observation period. As a result, she was considered the most suitable donor for directed blood donation to support the treatment of HDFN within the family.

Patient Follow-up

Over the three-year period, both Sister 1 and Sister 3 had live-born infants, delivered in the same year approximately three months apart. Following treatment for hyperbilirubinemia and anemia, both infants demonstrated normal growth and development, with no evidence of neurological abnormalities during follow-up. All the three sisters were enrolled into rare donor registry. The laboratory testing results over the three-year period are shown in Table 2.

Discussion

The absence of the Rh17 antigen, characteristic of the RhCE-null phenotype, is caused by rare RHCE variant alleles resulting from genetic alterations that inactivate or delete both copies of the RHCE gene.⁹⁻¹¹ Individuals with this genotype (D--/D--) lack expression of C/c and E/e antigens on red blood cell membrane but typically show enhanced expression of the D antigen.¹²

The frequency of the D-- haplotype varies among ethnic groups, with a higher prevalence reported in Japanese populations (0.0032) and American Hispanics (0.005).^{1,13} Individuals with this rare RhCE-null phenotype may develop the rare alloantibody anti-Rh17 when exposed to conventional RhCE antigens through pregnancy, transfusion, or transplantation. Once immunized, individuals with anti-Rh17 face significant clinical challenges, as demonstrated by the cases in this report. This antibody targets high-prevalence Rh17 antigens, which can lead to mild to severe HDFN or delayed hemolytic transfusion reactions.^{6-8,14}

Although cases of HDFN due to anti-Rh17 alloimmunization have been reported in the literature, this is the first documented report of multiple HDFN cases occurring among siblings within the same family. Notably, all high-risk pregnancies and cases of mild to severe HDFN occurred within a three-year period in a rural hospital setting.¹⁵ The hospital's blood bank team faced considerable challenges, including limited testing capabilities and restricted access to specialized

blood product preparation, while managing the care of this uniquely affected family. In collaboration with a tertiary healthcare facility and reference laboratories, the blood bank of a rural hospital developed a comprehensive management strategy for high-risk pregnancies and HDFN due to anti-Rh17 alloimmunization. As demonstrated in this family's cases, the

approach included prenatal monitoring, intra-uterine interventions, and postnatal management. A flowchart outlining this strategy is presented in Figure 1. Notably, this approach is also applicable to high-risk pregnancies and HDFN caused by other maternal red blood cell alloantibodies.

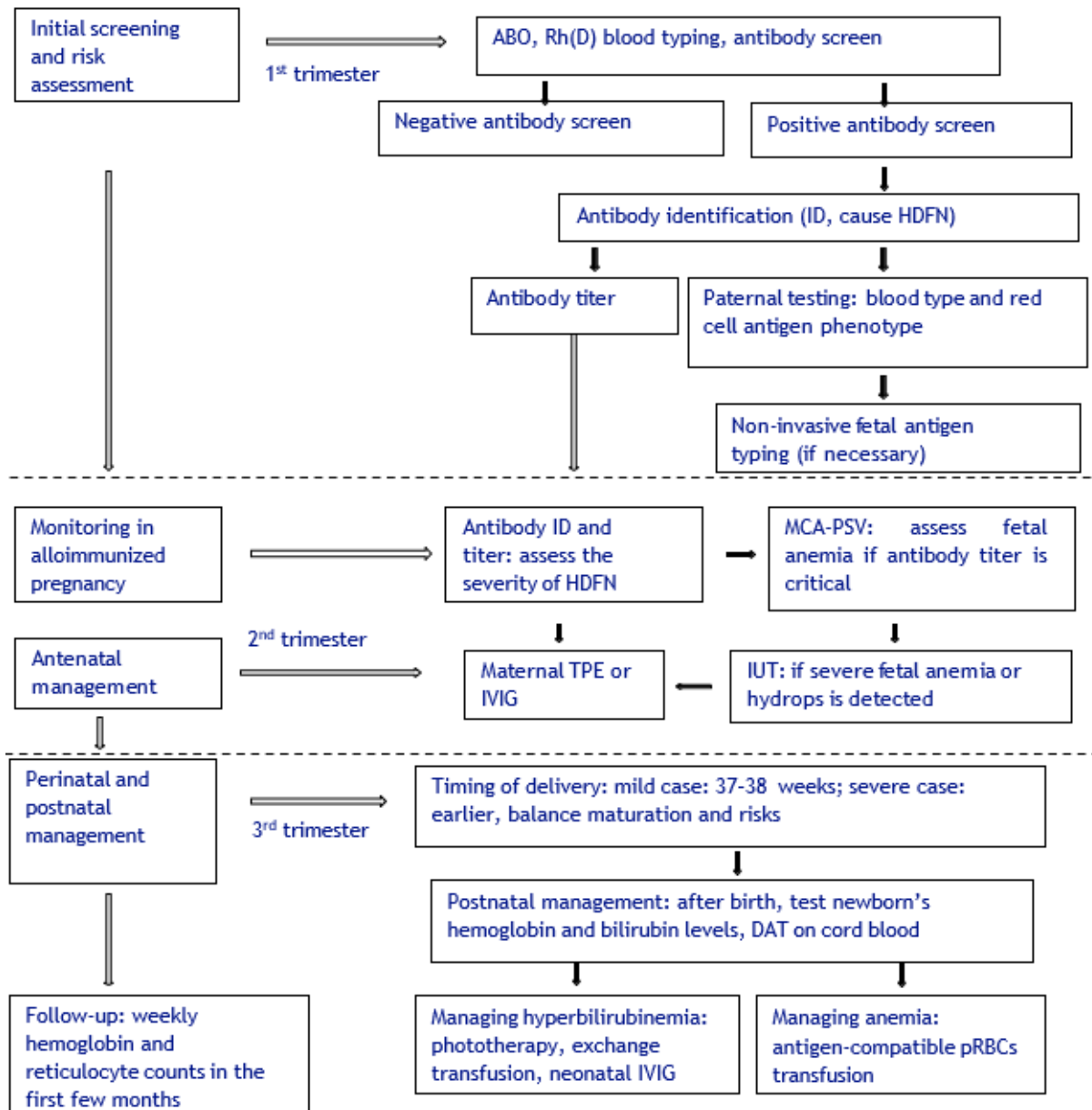


Figure 1. Flowchart for management of HDFN with maternal red blood cell antibody ABO, blood type; antibody ID, antibody identification; DAT, direct antiglobulin test; HDFN, hemolytic disease of the fetus and newborn; IUT intrauterine transfusion; IVIG, intravenous immunoglobulin; MCA-PSV, middle cerebral artery peak systolic velocity; pRBCs, packed red blood cells; Rh(D), RhD antigen; TPE, therapeutic plasma exchange.

During the first trimester of pregnancy, prenatal antibody screening, identification, and titration are essential for assessing the risk and potential severity of HDFN. If clinically significant antibodies are detected, paternal testing should be performed to determine the presence of the implicated red cell antigen and assess the likelihood of fetal antigen positivity.¹⁶ If the father is heterozygous for the antigen or if paternity is uncertain, non-invasive fetal antigen typing using cell-free fetal DNA from maternal blood should be considered to further evaluate fetal risk.¹⁶

During the second trimester, regular monitoring of maternal antibody titers is critical for assessing the severity of HDFN. For most clinically significant antibodies, a titer of 16 is considered the critical threshold.¹⁶ If titers reach or exceed this level, serial ultrasounds to measure the MCA-PSV are performed to detect fetal anemia.^{16,17} When MCA-PSV indicates severe anemia or if other signs of fetal hydrops are present, IUT is typically indicated. In particularly high-risk cases, such as Sister 1's second pregnancy, she was referred to a tertiary hospital for potential therapeutic plasma exchange (TPE).^{16,17} Unfortunately, her anti-Rh17 titer rose sharply within a short period, resulting in intrauterine fetal demise (IUFD) before TPE could be initiated.

In her subsequent pregnancy, a proactive approach was taken. The blood bank team coordinated with a reference laboratory's blood center to arrange directed donations of antigen-compatible red blood cells. These units were processed and cryopreserved in preparation for potential IUT.¹⁷ In addition, intravenous immunoglobulin (IVIG) may be considered to delay the need for IUT in certain cases.¹⁷

During the third trimester, delivery at a tertiary care center should be considered for high-risk pregnancies. The optimal timing of delivery requires balancing fetal lung maturity with the risks associated with ongoing hemolysis and IUTs. In milder cases, delivery is typically planned around 37-38 weeks of gestation,

while earlier delivery may be necessary for more severe cases, as seen in Sister 1's third pregnancy.^{15,18} Sister 3 developed anti-Rh17 during the third trimester of her first pregnancy, despite having no prior transfusion history - likely due to an anamnestic immune response.^{6,19}

Postnatal management for the newborns of Sister 1 and Sister 3 focused primarily on red blood cell transfusions to treat anemia and phototherapy to manage hyperbilirubinemia. In the event of severe hyperbilirubinemia, exchange transfusions using antigen-compatible pRBCs reconstituted with AB plasma should be prepared as a treatment option.^{20,21} In addition, neonatal IVIG may be administered to reduce red blood cell destruction and help delay or avoid the need for exchange transfusion.¹⁷

Finding a suitable donor for the RhCE-null phenotype is extremely challenging due to the rarity of this antigen profile. Fortunately, all three sisters in this family share the RhCE-null phenotype, making them valuable potential donors for rare donor registries. Sister 2, who has no history of pregnancy or transfusion and consistently negative antibody screens, stands out as the most ideal donor. Even in the presence of anti-Rh17 antibodies, washed maternal red blood cells can serve as an effective and safe source of blood for treating fetal anemia and hyperbilirubinemia, especially in emergency or resource-limited situations.^{7,21}

Conclusion

The cases reported here demonstrate that, despite the challenges of managing HDFN due to anti-Rh17 in a resource-limited rural setting, health care providers and laboratory professionals successfully treated the affected infants and managed complicated pregnancies through collaboration with tertiary healthcare facilities. This experience contributes valuable insight into the management of HDFN caused by anti-Rh17 antibodies.

Disclosure

The author declares no conflicts of interest.

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References

1. Daniels G. Rh and RHAG blood group systems in Human Blood Groups. 3rd ed. Wiley- Blackwell; 2013. <https://doi.org/10.1002/9781118493595.ch5>
2. Race RR, Sanger R, Selwyn JG. A probable deletion in a human Rh chromosome. *Nature*. 1950;166(4221):520. doi:10.1038/166520a0
3. Race RR, Sanger R, Selwyn JG. A possible deletion in a human Rh chromosome; a serological and genetical study. *Br J Exp Pathol*. 1951;32(2):124-135. PMID: PMC2073404
4. Vos GH, Vos D, Kirk RL, Sanger R. A sample of blood with no detectable Rh antigens. *Lancet*. 1961;1(7167):14-5. [https://doi.org/10.1016/S0140-6736\(61\)92183-3](https://doi.org/10.1016/S0140-6736(61)92183-3)
5. Salamat N, Bhatti FA, Hussain A, Ziaullah. Anti-Rh17 (anti-Hr₀): a rare diagnostic and management problem. *J Pak Med Assoc*. 2004;54(4): 215-8. PMID: 15242002
6. de Torregrosa MV, Rullan MM, Cecile C, Sabater A, Alberto C. Severe erythroblastosis in a primigravida associated with absence of Rh chromosomes. *Am J Obstet Gynecol*. 1961; 82(6):1375-8. [http://dx.doi.org/10.1016/s0002-9378\(16\)36267-6](http://dx.doi.org/10.1016/s0002-9378(16)36267-6)
7. Deitenbeck R, Tutschek B, Crombach G, Stannigel H. Successful management of pregnancy and hemolytic disease of the newborn due to anti-Hr₀ in a woman of the D- phenotype. *Transfusion*. 1999;39(10):1150-1. <https://doi.org/10.1046/j.1537-2995.1999.t01-1-39101150.x>
8. Aref K, Boctor FN, Pande S, Uehlinger J, Manning F, Eglowstein M, et al. Successful perinatal management of hydrops fetalis due to hemolytic disease associated with D- maternal phenotype. *J Perinatol*. 2002;22(8):667-8. <https://doi.org/10.1038/sj.jp.7210775>
9. Race RR, Sanger R. *Blood Groups in Man*, 6th ed. London: Blackwell Scientific Publications; 1975.
10. Cherif-Zahar B, Raynal V, Cartron JP. Lack of RHCE-encoded proteins in the D-- phenotype. *Blood*. 1996;88(4):1518-20. PMID: 8695878
11. Westhoff CM, Vege S, Nickle P, Singh S, Hue-Roye K, Lomas-Francis, C et al. Nucleotide deletion in RHCE*cE (907delC) is responsible for a D-- haplotype in Hispanics. *Transfusion*. 2011;51(10):2142-7. doi: 10.1111/j.1537-2995.2011.03144.x
12. Avent ND, Reid ME. The Rh blood group system: A review. *Blood*. 2000;95(2):375-87. <https://doi.org/10.1182/blood.V95.2.375>
13. Okubo Y, Tomita T, Nagao N, Yamaguchi H, Tanaka M. Mass screening donors for -D- and Jk(a-b-) using Groupamatic-360. *Transfusion*. 1983;23(4):362-3. <https://doi.org/10.1046/j.1537-2995.1983.23483276884.x>
14. Yun JW, Kang E-S, Ki C-S, Koh KC, Lim DW. Sensitization to multiple Rh antigens by Transfusion of random donor platelet concentrates in a -D- phenotype patient. *Ann Lab Med*. 2012;32(6):429-32. <http://dx.doi.org/10.3343/alm.2012.32.6.429>
15. Krumme AA, Suruki RY, Blacketer C, Hardin J, Swerdel JN, Tjoa ML et al. Characterization of severity of hemolytic disease of the fetus and newborn due to Rhesus antigen alloimmunization. *Am J Obstet Gynecol Glob Rep* 2025;5(1):100439.

<http://dx.doi.org/10.1016/j.xagr.2024.100439>

16. Dziegiel MH, Krog GR, Hansen AT, Olsen M, Lausen B., Norgaard LN et al. Laboratory Monitoring of Mother, Fetus, and Newborn in Hemolytic Disease of Fetus and Newborn. *Transfus Med Hemother*. 2021;48(5):306-15
<https://doi.org/10.1159/000518782>
17. Mimura K, Endo M, Takahashi A, Doi Y, Sakuragi M, Kiyokawa T, et al. Successful management of fetal hemolytic disease due to strong anti-Rh17 with plasma exchange and intrauterine transfusion in a woman with the D- phenotype. *Int J Hematol*. 2020;111(1):149-54.
<https://doi.org/10.1007/s12185-019-02735-6>
18. Mustafa HJ, Sambatur EV, Shamshirsaz AA, Johnson S, Moise KJ Jr, Baschat AA et al. Monitoring and management of hemolytic disease of the fetus and newborn based on an international expert Delphi consensus. *Am J Obstet Gynecol*. 2025;232(3):280-300.
<https://doi.org/10.1016/j.ajog.2024.11.003>
19. Hirose M, Nakanishi K, Kaku S, Moro H, Hodohara K, Aotani H, et al. Fetal hemolytic disease due to anti-Rh17 alloimmunization. *Fetal Diagn Ther*. 2004;19(2):182-6.
<https://doi.org/10.1159/000075147>
20. Abolhasan Choobdar F, Milani H, Behrouzi K, Khalesi N, Haghighi B, Manafi A, et al. Anti-Rh17 Alloimmunization: A rare case of severe hemolytic disease of the newborn and review of the literature. *J. Pediatr. Rev*. 2020;8(1):29-34.
<http://dx.doi.org/10.32598/jpr.8.1.29>
21. Denomme GA, Ryan G, Seaward PG, Kelly EN, Fernandes BJ. Maternal ABO-mismatched blood for intrauterine transfusion of severe hemolytic disease of the newborn due to anti-Rh17. *Transfusion*. 2004;44(9):1357-60.
<http://dx.doi.org/10.1111/j.1537-2995.2004.04082.x>

