INTERNATIONAL JOURNAL FOR INNOVATIVE RESEARCH IN MULTIDISCIPLINARY FIELD
ISSN(O): 2455-0620 [Impact Factor: 7.581]
Monthly, Peer-Reviewed, Refereed, Indexed Journal with IC Value : 86.87
Volume - 9, Issue - 6, June - 2023 Publication Date: 30/06/2023

DOIs:10.2015/IJIRMF/202306022 --:-- Research Paper / Article / Review

Overview of Present Conditions and Opportunities for Hemolytic Diseases in the Neonatal

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Abstract: *Erythroblastosis fetalis, often known as hemolytic disease of the newborn (HDN), is a hemolytic illness that mostly affects fetuses with rhesus positive blood and newborns with rhesus negative mothers. Due to rhesus or ABO incompatibility between the maternal and fetal blood, alloimmunization occurs, which causes maternal antibodies to assault fetal red blood cells. Prior to the development of immunoprophylactic medications, HDN was previously known to result in fetal mortality in one percent of all pregnancies, but if detected early, the disease is today reasonably successfully controlled with fewer difficulties. Serological tests, physical examinations, thorough history-taking, and imaging techniques such pelvic ultrasound scans are all required for the diagnosis. Pregnant Rh- women who have not been sensitized should get intravenous immunoglobulin (IVIG) sooner to stave against the illness. Understanding potential issues like severe hyperbilirubinemia and developing suitable solutions are equally important. Due to its high prevalence and complexity, HDN has been extensively studied, and new research on the illness is being done every year. To aid in future studies and evidence-based medical practice, this review discusses the disorder's an etiology, diagnosis, and treatment, including the most recent discoveries as of 2021. It also discusses trends and future directions.*

Key Words: *Alloimmunization, Fetomaternal hemorrhage, Hemolysis, Immunoprophylaxis.*

1. INTRODUCTION:

Erythroblastosis fetalis, commonly known as hemolytic disease of the newborn (HDN), is a hemolytic illness that mostly affects foetuses that test positive for the Rhesus virus (Rh+) and babies born to Rhesus-negative (Rh-) mothers. The condition was initially recorded in 1609 by a French midwife, but it wasn't until the 1950s that the fundamental reason was understood.(1) Due to the incompatibility of maternal and foetal blood based on the Rhesus and ABO antigen systems, the pathogenesis of HDN starts with the assault of foetal red blood cells (RBCs) by maternal antibodies. The mother typically begins producing anti-D antibodies through a process known as alloimmunization as she lacks the D antigen when the first child inherits the paternal D antigen, whose inheritance has been shown to follow an autosomal dominant pattern, and there occurs an event that leads to mixing of maternal and foetal blood.(2) In terms of immunology, antibody secretion begins with IgM, which cannot penetrate the placental barrier, and then isotype swapping, which results in the production of IgG antibodies. IgG antibodies are able to pass the placental barrier, and they do so during the second and/or subsequent pregnancies. They assault the foetal RBCs and result in hemolysis, which has a number of side effects such Hydrops fetalis and jaundice.(3) However, fetomaternal haemorrhage (FMH) is another way that IgG antibodies can get into the bloodstream of a foetus. According to estimates, 3 to 8 people out of every 100,000 suffer with HDN each year. 1% of all pregnancies had foetal loss as a result of it prior to the development of anti-D prophylaxis.(4) Although the prevalence of HDN is shown to vary with ethnicity, it is closely connected with the inheritance pattern in females that leads in the lack of the Rhesus (D) antigen.(5) As seen in Table 1, for instance, it has been discovered that whites have the highest incidence while Asians and American Indians have the lowest. Additionally, the D antigen is the most immunogenic Rh antigen that is currently recognised. About 10% of pregnant white women are Rh incompatible, according to estimates. HDN has been widely examined due to its great frequency and nature, and new studies are conducted every year, revealing new ideas about the illness. This review provides an overview of the disorder's aetiology, diagnosis, and treatment, taking into account the most current results as of 2021 as well as trends and future directions to support more research and evidence-based medical practise.

Table 1

Prevalence of HDN According to Ethnic Groups

Ethnicity	Prevalence by Percentage (%)
Africans	4
African-Americans	8
Whites	15–16
Eurasians	2.4
Asians	<1
Basque (Spain/France)	30–35

Fig. Table 1(5)

2. BACKGROUND:

In clinical practise, understanding blood group systems is crucial, particularly for haematological illnesses. The ABO and Rhesus systems are the two most common blood group systems in humans. The human blood types were discovered by Karl Landsteiner in 1904. He described them using the Landsteiner law, which asserts that for each blood type antigen that is not present on the RBCs, the equivalent antibodies are present in the plasma.(6) With the rhesus antigen, antigen D, this is not true. Normally, neither Rh+ nor Rh- persons have anti-D antibodies, nevertheless, when Rh- individuals are exposed to the D antigen, they begin secreting the appropriate antibodies. Therefore, RBC agglutination and hemolysis, which are the root causes of Rh incompatibility, can occur when a person has both D antigens and anti-D antibodies.(7) ABO incompatibility also follows the similar pattern, thus caution must be used while doing tissue transplants and blood transfusions. When alloimmunization takes place and maternal antibodies begin targeting foetal RBCs, Rh or ABO incompatibility between the mother and the foetus is nearly always the underlying cause of HDN. When IgG antibodies, as a result of antibody isotype switching, pass the placenta and enter the foetal circulation or through FMH, maternal antibodies reach the foetus.(2,8)

According to a 2017 assessment by Ree et al, HDN decreased globally from 1% with a 50% fatality rate before the advent of Rh-immunoprophylaxis in 1968 to 0.5% afterward. With the advent of antepartum Rh D immunoprophylaxis in 1970, occurrences further reduced to 0.1%. (9). Despite adequate RhD immunoprophylaxis, it is estimated that one to three Rh- women out of every 1,000 still experience alloimmunization nowadays.(10) The Rh- phenotype is less frequent, while being more prevalent in some ethnic groups and races than others, even though Rh incompatibility accounts for a bigger part of HDN. For instance, epidemiological research has shown that just 1% of Asians and 15% of Whites have Rh- (Table 1). The pathophysiology of HDN can be explained by the aforementioned processes. ABO mismatch reportedly impacts 15 to 25% of all pregnancies, according to published studies. Only 1% of people will really get HDN, though. (11) ABO incompatibility results in a mild reaction, which is most likely a result of the expression of ABO blood type antigens and their presentation in various organs. Following the mixing of maternal and blood, maternal antibodies are released in FMH. The Rhesus/D antigen is the most often involved antigen. (12) Maternal blood, which is Rh-, does not contain the antigens present in foetal blood, which are mostly Rh-positive and inherited from the paternal side. Since IgM-type antibodies are the first to develop as a result of FMH, the first pregnancy survives and is left with an immune system that has already been sensitised.(12) The foetus is in danger if there is rhesus factor incompatibility. In later stages, the mother's rhesus antibodies may target the fetus's antigens in successive pregnancies, leading to alloimmune hemolysis in the foetus. As a result of the fetus's haemoglobin being broken down, a substantial amount of bilirubin is released. They are delivered to the maternal circulation by the placenta. Once they are within the mother's system, she works on them and gets rid of them. (13,14) However, issues might arise, raising serum bilirubin levels and causing severe jaundice.

The hemolysis caused by the rhesus antibodies may cause moderate anaemia in the least affected neonates and just hyperbilirubinemia. Roughly 25% of cases of foetal hyperbilirubinemia result in kernicterus. (15,16) Bilirubin accumulation in the tissues of the central nervous system results in the disease known as kernicterus. Typically, it occurs soon after delivery. Because kernicterus survivors may still suffer developmental delays, hypotonia, and hearing loss, they are often not regarded as actual survivors. (17) As a result, during the newborn's physical examination, the previously listed symptoms should be looked for. The importance of the history and physical examination cannot be emphasised in any diagnosis. Risk factors for FMH include antepartum haemorrhage, chorionic villus sampling, amniocentesis, miscarriages, abortions, and maternal blood transfusions. Previous histories of HDN or hydrops fetalis are also a risk factor.(18) It is crucial to do blood tests throughout the first trimester. Blood type O pregnant women should have thorough prenatal and postpartum examinations. It is suggested that parents find out their child's blood type

as soon as possible after delivery. To rule out the possibility of HDN, a woman with the blood type Rh- undergoes the Rosette test.(19)This test can detect alloimmunization brought on by even minute FMH. A second test called Kleihauer-Betke acid elution is carried out if there is a clinical suspicion of FMH (>30 mL blood).(19) In this test, the number of foetal RBCs in the woman's blood is quantified. To determine whether another Rh IgG injection is required, a comparable test might be utilised. Pelvic ultrasonography, which is frequently limited to the pelvis, is crucial for the diagnosis of HDN in pregnant women with likely Rh incompatibility.(13,20)Before a clear HDN diagnosis can be made, other causes of infant jaundice and anaemia must be ruled out. As a consequence, both the Gel card method and conventional tube procedures may be employed for diagnosis.(21,23) Two established methods are the direct and indirect Coombs tests. In the indirect Coombs test, the red blood cells are centrifuged and washed with antihuman antiglobulin. When immunoglobulins or complement factors are attached to the surface of RBCs in vitro, a positive test result is indicated by agglutination.(24,25) The indirect Coombs test is utilised in prenatal screening to identify antibodies produced during pregnancy as well as testing prior to blood transfusion. It makes use of the patient's serum, which has been incubated with known antigenic foreign red blood cells.The Coombs reagent is then introduced, and the test is considered positive if agglutination takes place. In the Red blood cell test, the serum is incubated, and the reaction takes place inside a microtube. While larger agglutinates stay on top, non-agglutinated cells flow through a gel matrix (Sephadex) to generate a bottom.(26) Singh et al. found that while comparing and contrasting gel card technology with conventional techniques, the sensitivity and specificity of the two systems were equal. The gel card method, on the other hand, required less time, was more reliable, and allowed for the documentation of the results.(27)

Before preventative and curative methods like phototherapy, intrauterine transfusion, exchange transfusion, and amniocentesis were developed, the illness was responsible for a sizable amount of morbidity and mortality. With a perinatal survival rate of above 90%, the incidence has since declined.(28) Since it has fewer adverse effects and is effective in treating preterm newborns, phototherapy has been the first-line treatment technique of choice for more than 30 years.(29,30) Prophylactic and therapeutic phototherapy are the two types of treatment that are provided. Maximum exposure to the infant's body, appropriate irradiance, and light emission in the blue-green spectrum between 460 and 490 nm all contribute to this kind of therapy.(29,31,32)HDN-induced hyperbilirubinemia is often treated with phototherapy and, rarely, exchange transfusion. Children with the following birth weights and bilirubin levels were recommended as having a chance of developing HDN in a 2004 study by paediatricians (AAP): 2000 g, 2000 to 2499 g, and 2500 g, respectively(13,33). However, exchange transfusion, which involves swapping out the baby's RBCs with antigen-negative RBCs, is advised for neonates who are highly anaemic.(34) Additionally, an ABO-matched packed RBC blood transfusion for frail individuals may be investigated.(35) According to studies, exchange transfusion is likewise risk-free, with child mortality rates ranging from 0.53% to 4.7%.(29,26) Severe cardiorespiratory difficulties, catheter and blood product issues, metabolic disturbances, necrotizing enterocolitis, and intestinal perforation are among adverse consequences of exchange transfusion. The risks associated with exchange transfusions have been estimated to be as high as 74% during the preceding two decades. However, the detrimental effect is about 31%. According to Steiner et al., there hasn't been an increase in morbidity or death for more than 21 years.(37) With some benefits, intravenous immunoglobulin (IVIG) has been suggested as a substitute for exchange transfusion and phototherapy. However, the efficacy of intravenous immunoglobulin prophylaxis is still in question. According to several studies, exchange transfusion, a more invasive method, offers no advantage over IVIG.(9,30,38)

Clinical data also indicate that IVIG has not successfully treated a significant proportion of ABO-HDN patients.(29,34) IgG, IgM, IgA, and IgE are the main antibodies found in IVIG, along with electrolytes, sugar, cytokines, albumin, and solvents. According to the IVIG's postulated mechanisms, it reduces the danger in babies with ABO-HDN by preventing antibody neutralisation.(39,40) All of the aforementioned treatment methods, however, have drawbacks. As a result, prevention continues to be crucial in reducing morbidity and death. Additionally, early screening and preventative measures are necessary during prenatal care consultations due to concerns about the severity of issues and the mortality risk. In addition, anti-D immunoglobulin prophylaxis should be used after sensitising operations such abortion, amniocentesis, and chorionic villus sampling.(41,42) Neil Murray of ADC Foetal and Neonatal claims that it has been found that the HDN's spectrum has expanded since it was originally recognised.(43) In the past, the condition was unchanging, leading to increased foetal and neonatal hemolysis, hyperbilirubinemia, and severe anaemia. However, this syndrome has been greatly reduced when Rh- women get routine postnatal prophylactic anti-D immunoglobulin. One of the most successful post-modern perinatal care choices has shown to be this treatment.(41) Blood transfusions are necessary for anaemic babies; the blood must fit ABO specifications and have a sufficient quantity of red blood cells. The blood also has to be type O, Rh, leukodepleted, and irradiated.(19) Throughout the speech, each of these has to be present.

3. ETIOLOGY:

The incompatibility of the mother's and the baby's blood is a common cause of HDN. The mother's immune system recognises the foetal antigens as non-self and opposes them by generating antibodies that do not think twice about attacking and destroying them. Let's say the baby's blood crosses across and enters her incompatible RBCs.(2) During pregnancy or childbirth, the cross-over typically takes place through the placenta. This causes serious problems with the baby's system that might potentially result in the infant's eventual death. The mother's immune system does not, however, eliminate the antibodies. Nevertheless, it creates immunological memory, which may result in the release of more antibodies following re-exposure to the antigen. Therefore, even after a loss or abortion, HDN is likely to happen in the second and future pregnancies (8).

4. DIAGNOSIS:

Laboratory Studies

It takes a lot of laboratory and imaging experience to diagnose and treat pregnant women with HDN. Rapid and severe hyperbilirubinemia or chronic hyperbilirubinemia, as well as hemolysis on blood film findings, are clinical indicators of HDN.It should be emphasised that the severity of the illnesses is influenced by the level of hematopoiesis (44) as well. Additionally, individuals frequently exhibit clinical disorders including anaemia, thrombocytopenia, and neutropenia. Arteriole samples can be used to assess the anaemia rather than capillary blood. Exchange transfusions are frequently accompanied by thrombocytopenia. It happens when blood platelets do not develop properly and when erythropoiesis takes precedence over platelet creation. Most often, neutropenia is seen following intrauterine transfusion. It is frequently accompanied by reticulocytosis, or an increase in nucleated RBCs and cell fragmentation, as well as elevated levels of circulating cytokines (such granulocyte-macrophage colony-stimulating factor).(36,45) Additionally, erythroblasts, polychromasia, anisocytosis, and the absence of spherocytes are frequently seen in Rh-HDN peripheral blood smears.(4) Additionally, a serological test must be performed to confirm the HDN's positive. The outcome of this test may indicate if the mother's Coombs and antibody variations have an influence on the infant directly or indirectly. An impactful finding from the natural antibody test has a predictive value of 23% and a sensitivity of 86%, according to a recent research.(46) The direct antibody test may come out negative if antic is the aetiology of newborn hemolytic syndrome. It is advised that a diagnosis only be established if the indirect Coombs test has demonstrated certainty. The laboratory tests used to diagnose HDN are listed in Table 2 along with the predicted outcomes.

Table 2

Laboratory Tests and Results for HDN

Mother's Sample		Baby's Sample	
Test	**Result**	**Test**	**Result**
ABO/Rh Determination	A (Rh D positive)	ABO/Rh Determination	A (Rh D positive)
Antibody Screening	Positive	Polyspecific DAT	Positive
Antibody Identification	Anti-c testing	IgG/C3 Coombs	IgG positive/C3d-negative
Antigen Typing	Negative for "c" antigen	Elution	Positive

Figure: Table 2 (47)

Imaging Studies:

The foetus should undergo prenatal testing for mother red cell alloantibodies. Additionally, ultrasound should be used, particularly when an intravenous transfusion is administered.During this stage, maternal blood samples should be checked for ABO, Rh group, and red blood cells. If HDN-causing alloantibodies are discovered, a laboratory test should be run to confirm the results. To calculate the likelihood that a newborn will have the correct red cell antigen, the phenotype of the father should be determined.(49) Following confirmation of foetal Rh positive, foetal monitoring can be carried out using serial maternal pelvic ultrasounds, umbilical artery, and middle cerebral artery (MCA) dopplers. MCA dopplers are frequently used to check Rh+ foetuses for anaemia.Since the 24th week of pregnancy, they are performed every one to two weeks. Peak systolic velocity (PSV), which is always going to rise in anaemia, is what this type of monitoring looks for.(50) If the foetus is severely damaged, foetal ultrasounds are often used to screen for foetal ascites, soft-tissue edoema, scalp edoema, pleural effusion, cardiomegaly, and hepatomegaly with portal hypertension (51).

Patient Care and Prevention:

Group O negative blood transfusion should start when test findings show uterine anaemia. The maternal blood should be cross-matched with the transfused blood type O negative. The optimal time to get this operation is between the ages of 16 and 18.(52) Additionally, although intravenous transfusion is straightforward in a hydropic foetus and has fewer issues than intraperitoneal foetal transfusion, it need to be employed whilst being monitored by ultrasonography.(53) After delivery, neonates should be closely monitored to check for the onset of any late anaemia between six and eight weeks. This represents half of the total. However, the common sickness that requires transfusion affects about 25% of babies.(54) A paediatrician with specialised expertise in newborn resuscitation should deliver the baby if severe HDN is anticipated, and fresh blood should be made accessible. The risk of hemolysis and the need for exchange transfusion are reduced the earlier IVIG is administered.(55) IVIG should be administered to all Rh- women who have not yet been sensitised in order to avoid HDN. A strong relationship between clinicians and patients is necessary to improve health care outcomes. Collaboration is also required among the interprofessional team members, which mostly comprises of an obstetrician, a primary care physician, and nurses. Doctors must thoroughly screen and precisely assess both the mother and the father during the first trimester since this illness is preventable, and they must closely watch the antibody titers in Rh- females. These antibody levels should be less than 1:16, and invasive testing is done to address them properly if they are greater.(56) Use of MCA for critical foetal monitoring Doppler gives a precise image of foetal anaemia, allowing doctors to decide whether or not an intrauterine transfusion is necessary.

Potential Complications of Exchange and Transfusion:

A blood transfusion may result in a number of problems. To build solutions and manage such potential issues, it is essential to have a basic awareness of them. ABO incompatibility, prolonged hyperbilirubinemia, and severe hyperbilirubinemia—all of which are unpredicted by maternal prenatal antibody screening—are a few of the problems.(57) A woman who has antibodies also runs the risk of developing a transfusion reaction if she requires a blood transfusion in the future. Informing physicians and medical workers about her prior diagnoses is an alternative course of action. This might make it easier for doctors to diagnose and treat patients correctly. During pregnancy, a foetus may experience mild to severe anaemia or even jaundice. Additionally, the infant runs the danger of having hydrops fetalis if its organs are unable to cope with anaemia.(58) At delivery, the infant may experience kernicterus, the most severe form of hyperbilirubinemia. HIV, hepatitis, and malaria are examples of bacterial and viral illnesses that might have negative effects under specific circumstances. There might also be metabolic issues such acidosis, hypocalcemia, and hypernatremia.(59) In addition, thrombosis, neutralising enterocolitis, and umbilical vessel perforation are also possible vascular issues. Another concomitant systemic risk that seriously damages the tissues is hypothermia.(60)Some of the aforementioned possible dangers are summarised in Table 3.

Table 3

The Potential Complications Associated with HDN

Outcome	Number (%)
Cardiovascular	
Bradycardia (mild)	1 (2)
Bradycardia needing CPR	1 (2)
Limb cyanosis	1 (2)
Metabolic	
Hypomagnesemia	2 (4)
Hyperglycemia	7 (15)
Hematologic	
Thrombocytopenia	15 (32)
Platelet Transfusion	3 (7)
Anemia	11 (23)
PRBCs Transfusion	4 (8)
Follow-up and neurological complications	
Post-discharge visit for at least 1 time	35 (78)
Post-discharge follow-up for more than one year of age	25 (52)
Developmental delay and seizures	1 (4)
Spasticity	1 (4)
Hearing Deficit	1 (4)

Trends and Future Prospects:

The use of molecular techniques for blood type is increasing as molecular testing becomes more prevalent in medicine. In certain people, serological probes don't always accurately detect the RhD type. The most prevalent genetic background that seems to explain this serological typing issue is weak D phenotypes. In order to provide precise and useful findings for RhD blood typing and Rh Ig administration for patients with a weak D phenotype, academics have recently pushed for the use of RhD genetic testing.(63,65) Both in wealthy and developing nations, there is still much need for enhancing HDN management. A excellent place to start would be with universal, evidence-based recommendations for intrauterine or preconception RBC antigen matching transfusion methods.(66) The mechanism of action of Rh immunoglobulin is a crucial field that requires more study. We think that a thorough comprehension of the functions of RBC clearance, antigen masking, modulation, and immune suppression might aid in the creation of creative preventative prophylactic for immunisation against Rh and non-Rh antigens during gestation. The development of creative preventative therapies during pregnancy for immunisation against RhD and non-RhD antigens may benefit from a thorough understanding of the roles played by foetal RBC clearance, antigen masking, antigen modulation, and immune suppression in the effectiveness of Rh immunoglobulin. More knowledge of the significance of anti-RhD or other alloantibody glycosylation patterns may also be helpful in predicting the clinical significance of existing maternal alloantibodies and in the development of innovative therapies. The need for therapies other than intrauterine infusions to reduce the hazards that maternal alloantibodies provide to the foetus is another area of need.

5. CONCLUSION :

HDN is a multifaceted, complicated illness that presents with special technical challenges during a number of formative prenatal and neonatal developmental phases. The introduction of IVIG, IUT, and noninvasive foetal genetic testing, among other developments in maternal-fetal medicine, have significantly improved HDN outcomes and prevented maternal allosensitization. Women and their children who have blood group incompatibilities will benefit from future developments in blood typing and noninvasive testing. Additionally, the racial and ethnic groups who are most at danger need to receive greater attention.

REFERENCES:

1. Jackson ME, Baker JM. Hemolytic disease of the fetus and newborn: historical and current state. *Clin Lab Med*. 2021;41(1):133–151. doi: 10.1016/j.cll.2020.10.009
2. Gupta GK, Balbuena-Merle R, Hendrickso JE, Tormey CA. Immunohematologic aspects of alloimmunization and alloantibody detection: a focus on pregnancy and hemolytic disease of the fetus and newborn. *Transfus Apheresis Sci*. 2020;10:102946
3. Alaqeel AA. Hyporegenerative anemia and other complications of rhesus hemolytic disease: to treat or not to treat is the question. *Pan Afr Med J*. 2019;32:134
4. Routray SS, Behera R, Mallick B, et al. The spectrum of hemolytic disease of the newborn: evaluating the etiology of unconjugated hyperbilirubinemia among neonates pertinent to immunohematological workup. *Cureus*. 2021;13(8):110
5. Doll P. Hemolytic disease of newborn: symptom and causes. *Pediatrics*. 2021;132(3):e145–e232. doi: 10.2342/peds.114.2.e143
6. Cowan H. The discovery of human blood groups: Karl Otto Landsteiner. *Br J Cardiac Nursing*. 2017;12(6):290–292. doi: 10.12968/bjca.2017.12.6.290
7. Akkök ÇA, Seghatchian J. Immunohematologic issues in ABO-incompatible allogeneic hematopoietic stem cell transplantation. *Transfus Apheresis Sci*. 2018;57(6):812–815. doi: 10.1016/j.transci.2018.10.020
8. Wang R, Li Y, Tong Y, Su N. Hemolytic disease of the fetus and newborn caused by anti-group A IgG from a group B mother. *J Pediatr Hematol Oncol*. 2021;43(6):e785–e787. doi: 10.1097/MPH.0000000000001948
9. Ree IM, Smits-Wintjens VE, van der Bom JG, van Klink JM, Oepkes D, Lopriore E. Neonatal management and outcome in alloimmune hemolytic disease. *Expert Rev Hematol*. 2017;10(7):607–616. doi: 10.1080/17474086.2017.1331124
10. Basu S, Kaur R, Kaur G. Hemolytic disease of the fetus and newborn: current trends and perspectives. *Asian J Transfus Sci*. 2011;5(1):3. doi: 10.4103/0973-6247.75963
11. Kurian R. *To Study the Prevalence of ABO Incompatibility in O Blood Group Mothers and Assessment of IgG Subclasses (IgG1 and IgG3) in them and its Correlation with Occurrence and Severity of ABO Hemolytic Disease of Newborn (ABO-HDN) in a Tertiary Health Care Centre in South India [Doctoral dissertation]*. Vellore: Christian Medical College; 2020

12. Tao E, Ye D, Long G, et al. Severe neonatal anemia affected by massive fetomaternal hemorrhage: a single-center retrospective observational study. *J Maternal-Fetal Neonatal Med*. 2020;1–7. doi: 10.1080/14767058.2020.1845313
13. Zwiers C, Scheffer-Rath ME, Lopriore E, de Haas M, Liley HG. Immunoglobulin for alloimmune hemolytic disease in neonates. *Cochrane Database Syst Rev*. 2018;2018(3):e235. doi: 10.1002/14651858.CD003313.pub2
14. Calhoun DA, Mahoney DH Jr. Postnatal diagnosis and management of hemolytic disease of the fetus and newborn; 2018.
15. Pichon JBL, Riordan SM, Watchko J, Shapiro SM. The neurological sequelae of neonatal hyperbilirubinemia: definitions, diagnosis, and treatment of the kernicterus spectrum disorders (KSDs). *Curr Pediatr Rev*. 2017;13(3):199–209.
16. Watchko JF. Neonatal indirect hyperbilirubinemia and kernicterus. In: Christine A. Gleason and Sandra E. Juul, editor, *Avery's Diseases of the Newborn*. Elsevier; 2018:1198–1218.
17. Usman F, Diala UM, Shapiro S, LePichon JB, Slusher TM. Acute bilirubin encephalopathy and its progression to kernicterus: current perspectives. *Res Rep Neonatol*. 2018;8:33. doi: 10.2147/RRN.S125758
18. Akorsu EE, Acquaye JK, Benneh AA, Oppong SA, Olayemi E. Fetomaternal hemorrhage among pregnant women in Accra, Ghana. *Int J Gynecol Obstet*. 2019;146(3):333–338. doi: 10.1002/ijgo.12890
19. Hall V, Avulakunta ID. *Hemolytic Diseases of the Newborn*. StatPearls [Internet]; 2021.
20. Adam DL, Bowes L, Goodyear L, Moorehead PC. Conservative management of hyperferritinemia in the fetus and newborn hemolytic disease: a case report and review of the literature. *J Pediatr Hematol Oncol*. 2021;43(2):73–76. doi: 10.1097/MPH.0000000000001586
21. Kumawat V, Kulkarni K, Goyal M, Lokadas V. ABO hemolytic disease of the fetus and newborn; still a diagnostic dilemma: a case report. *Indian J Hematol Blood Transfus*. 2018;34(1):183–184. doi: 10.1007/s12288-017-0792-1
22. Jain A, Malhotra S, Marwaha N, Kumar P, Sharma RR. Severe ABO hemolytic disease of fetus and newborn requiring blood exchange transfusion. *Asian J Transfus Sci*. 2018;12(2):176. doi: 10.4103/ajts.AJTS_106_17
23. Subramaniyan R. Blocked D in RhD hemolytic disease of fetus and newborn. *Global J Transfus Med*. 2019;4(1):114.
24. Haider M, Memon S, Tariq F, Fatima S, Hameed A. Rhesus isoimmunization: late-onset hemolytic disease of the newborn without jaundice. *Cureus*. 2020;12(1):111.
25. Ajmani PS. Hemolytic disease of the newborn. In: *Immunohematology and Blood Banking*. Singapore: Springer; 2020:103–117.
26. Bi SH, Jiang LL, Dai LY, et al. Rh-incompatible hemolytic disease of the newborn in Hefei. *World J Clin Cases*. 2019;7(20):3202. doi: 10.12998/wjcc.v7.i20.3202
27. Singh R, Garg P, Sucheta KA, Babra M. Comparison between conventional tube method and gel card technique for blood cross-matching: a study in a tertiary care center of north India. *Int J Res Pharm Sci*. 2020;11(4):6500–6503. doi: 10.26452/ijrps.v11i4.3529
28. Moise KJ Jr. Management of rhesus alloimmunization in pregnancy. *Obstet Gynecol*. 2002;100(3):600–611. doi: 10.1016/s0029-7844(02)02180-4
29. Al-Lawama M, Badran E, Ala'Elrimawi ABM, Alkhatib H. Intravenous Immunoglobulins as adjunct treatment to phototherapy in isoimmune hemolytic disease of the newborn: a retrospective case-control study. *J Clin Med Res*. 2019;11(11):760.
30. Pan J, Zhan C, Yuan T, et al. Intravenous immunoglobulin G in the treatment of ABO hemolytic disease of the newborn during the early neonatal period at a tertiary academic hospital: a retrospective study. *J Perinatol*. 2021;4:1–6.
31. AlKhater SA, Albalwi RA, Alomar SA, et al. Value of the direct antiglobulin test in predicting the need for phototherapy in newborns. *J Blood Med*. 2021;12:53. doi: 10.2147/JBM.S291606 32. Krog GR, Donneborg ML, Hansen BM, et al. Prediction of ABO hemolytic disease of the newborn using pre-and perinatal quantification of maternal anti-A/anti-B IgG titer. *Pediatr Res*. 2020;15:1–8.
32. Tewari VV, Kumar A, Singhal A, et al. Evaluation of Rh-hemolytic disease in neonates and management with early intensive phototherapy in the neonatal intensive care unit. *J Trop Pediatr*. 2020;66(1):75–84.
33. Metcalf RA, Khan J, Andrews J, Mayock D, Billimoria Z, Pagano MB. Severe ABO hemolytic disease of the newborn requiring exchange transfusion. *J Pediatr Hematol Oncol*. 2019;41(8):632–634. doi: 10.1097/MPH.0000000000001248

34. El Fekey SWI, El-Sharkawy HM, Ahmed AAEE, Nassar MAE, Elgendy MM. Effect of intravenous immunoglobulin in reducing bilirubin levels in hemolytic disease of newborn. *Egypt J Hospital Med*. 2019;74(5):957–968. doi: 10.21608/ejhm.2019.25779
35. Mimura K, Endo M, Takahashi A, 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):149–154. doi: 10.1007/s12185-019-02735-6
36. Steiner LA, Bizzarro MJ, Ehrenkranz RA, Gallagher PG. A decline in the frequency of neonatal exchange transfusions and its effect on exchange-related morbidity and mortality. *Pediatrics*. 2007;120(1):27–32. doi: 10.1542/peds.2006-2910
37. Venkataraman R, Yusuf K. Intravenous immunoglobulin in the management of a rare cause of hemolytic disease of the newborn: anti-SARA antibodies. *J Neonatal Perinatal Med*. 2017;10(3):329–332. doi: 10.3233/NPM-16131
38. Maisonneuve E, Toly-Ndour C, Jouannic JM. Postponing early intrauterine transfusion with intravenous immunoglobulin treatment: the PETIT study on the severe hemolytic disease of the fetus and newborn. *Am J Obstet Gynecol*. 2019;220(3):288. doi: 10.1016/j.ajog.2018.10.025
39. Hughes GO, Osman J, Coady AM, Klonin H. Acute hemoglobin increase after transfusion and immunoglobulin for rhesus hemolytic disease of the newborn. *J Clin Neonatol*. 2018;7(1):48. doi: 10.4103/jcn.JCN_48_17
40. Mark A, Foster AM, Grossman D, et al. Foregoing Rh testing and anti-D immunoglobulin for women presenting for early abortion: a recommendation from the National Abortion Federation's Clinical Policies Committee. *Contraception*. 2019;99(5):265–266. doi: 10.1016/j.contraception.2019.02.008
41. de Haas M, Thurik FF, van der Ploeg CP, et al. Sensitivity of fetal RhD screening for safe guidance of targeted anti–D immunoglobulin prophylaxis: prospective cohort study of a nationwide programme in the Netherlands. *Obstet Gynecol Surv*. 2017;72(3):155–157. doi: 10.1097/01.ogx.0000513227.69777.ca
42. Sahoo T, Thukral A, Sankar MJ. Delayed cord clamping in Rh-alloimunised infants: a randomized controlled trial. *Eur J Pediatr*. 2020;179(6):297–316. doi: 10.1007/s00431-020-03578-8
43. Koelewijn JM, Slootweg YM, Folman C, van Kamp IL, Oepkes D, de Haas M. Diagnostic value of laboratory monitoring to predict severe hemolytic disease of the fetus and newborn in non-D and non-K-alloimmunized pregnancies. *Transfusion*. 2020;60(2):391–399. doi: 10.1111/trf.15631
44. Slootweg YM, Lindenburg IT, Koelewijn JM, Van Kamp IL, Oepkes D, De Haas M. Predicting anti-kell-mediated hemolytic disease of the fetus and newborn: diagnostic accuracy of laboratory management. *Am J Obstet Gynecol*. 2018;219(4):393–e1. doi: 10.1016/j.ajog.2018.07.020
45. Leafy MS, Ellarby NS. Early intravenous immunoglobulin. *Eur J Pediatr*. 2020;170(4):461–467. doi: 10.1007/s00431-010-1310-8.Epub.2019
46. Elalfy MS. Prevention of hemolytic disease of newborn. *Eur J Pediatr*. 2018;170(4):461–467. doi: 10.1007/s00431-010-1310-8
47. Osonoi K, Kudo K, Kobayashi A, et al. A comprehensive evaluation including ultrasound monitoring of fetal hemolytic disease in Rhesus E incompatibility. *Hirosaki Med J*. 2020;71(1):71–74.
48. Agrawal A, Hussain KS, Kumar A. Minor blood group incompatibility due to blood groups other than Rh (D) leading to hemolytic disease of the fetus and newborn: a need for routine antibody screening during pregnancy. *Intractable Rare Dis Res*. 2020;60:1094–2019.
49. Santavy J. Hemolytic disease in the newborn–history and prevention in the World and the Czech Republic. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2010;154(2):147–151. doi: 10.5507/bp.2010.022
50. Peyrard T, Pham BN, Arnaud L, et al. Fatal hemolytic disease of the fetus and newborn associated with anti-Jra. *Transfusion*. 2008;48(9):1906–1911. doi: 10.1111/j.1537-2995.2008.01787.x
51. Noronha SA. Acquired and congenital hemolytic anemia. *Pediatr Rev*. 2016;37(6):235–246. doi: 10.1542/pir.2015-0053
52. Perinatal J. Intravenous Immunoglobulin G in treating ABO hemolytic disease of the newborn. *Indian J Hematol Blood Transfus*. 2021;132(3):e145–e232. doi: 10.2342/peds.114.2.e143
53. Crowe EP, Goel R. Survey of newborn direct antiglobulin testing practice in US and Canadian transfusion services. *Transfusion*. 2021;120(1):27–32. doi: 10.1542/peds.2006-2910
54. Wang N, Zhang L. A case of severe hemolytic disease of the newborn. *N Engl J Med*. 2021;37(1):1775–1777. doi: 10.1056/NEJM199812103392410

55. Maisonneuve E, Dugas A, Friszer S, et al. Effect of intravenous immunoglobulins to postpone the gestational age of first intrauterine transfusion in very severe red blood cell alloimmunization: a case-control study. *J Gynecol Obstet Human Reprod*. 2021;50(7):102119. doi: 10.1016/j.jogoh.2021.102119
56. Bussel JB, Vander Haar EL, Berkowitz RL. New developments in fetal and neonatal alloimmune thrombocytopenia. *Am J Obstet Gynecol*. 2021;225:120–127. doi: 10.1016/j.ajog.2021.04.211
57. Pegoraro V, Urbinati D, Visser GH, et al. Hemolytic disease of the fetus and newborn due to Rh (D) incompatibility: a preventable disease still produces significant morbidity and mortality in children. *PLoS One*. 2020;15(7):e0235807. doi: 10.1371/journal.pone.0235807
58. Bujandric N, Grujic J. Exchange transfusion for severe neonatal hyperbilirubinemia: 17 years experience from Vojvodina, Serbia. *Indian J Hematol Blood Transfus*. 2016;32(2):208–214. doi: 10.1007/s12288-015-0534-1
59. Hendrickson JE, Delaney M. Hemolytic disease of the fetus and newborn: modern practice and future investigations. *Transfus Med Rev*. 2016;30(4):159–164. doi: 10.1016/j.tmrv.2016.05.008
60. Delaney M, Matthews DC. Hemolytic disease of the fetus and newborn: managing the mother, fetus, and newborn. *Hematology*. 2015;2015(1):146–151. doi: 10.1182/asheducation-2015.1.146
61. Mitra S, Rennie J. Neonatal jaundice: etiology, diagnosis, and treatment. *Br J Hosp Med*. 2017;78(12):699–704. doi: 10.12968/hmed.2017.78.12.699
62. Fasano RM. Hemolytic disease of the fetus and newborn in the molecular era. *Semin Fetal Neonatal Med*. 2016;21(1):28–34. doi: 10.1016/j.siny.2015.10.006
63. Quraishy N, Sapatnekar S. Advances in blood typing. *Adv Clin Chem*. 2016;77:221–269.
64. Chen DP, Wen YH, Lu JJ, Tseng CP, Wang WT. Rapid rare ABO blood typing using a single PCR based on a multiplex SNaPshot reaction. *J Formosan Med Assoc*. 2019;118(1):395–400. doi: 10.1016/j.jfma.2018.06.014
65. Zhou ZZ, Xu D, Sun L, Lan J. The progress in pre-transfusion test technique research. *Asia Pac J Blood Types Genes*. 2017;1:7–12.